STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 192068

TO: Dwayne C Jones **Location: REM/3B87/3C70** **Art Unit: 1614** **June16, 2006** **Case Serial Number: 10/529784**	**From: P. Sheppard** **Location: Remsen Building** **Phone: (571) 272-2529** **sheppard@uspto.gov**

Search Notes

ACCESS DB # 192068

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Dwayne C. Jones Examiner # : 71244 Date: 05/30/00

Art Unit: 1614 Phone Number: 2- 0575 Serial Number: 10/529,724

Location (Bldg/Room#): 3B87 (Mailbox #): 3C70 Results Format Preferred (circle): PAPER DISK

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REM

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: see attached sheet

Inventors (please provide full names): "

"

Earliest Priority Date: "

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claims 7-10

10/529,754

IN THE CLAIMS

Please amend the claims as follows:

Claims 1-6 (Canceled).

Claim 7 (Original): A method of preventing or treating a neurodegenerative disease, which comprises administering an effective amount of N-acetyl-L-pipecolic acid or a pharmaceutically acceptable salt thereof.

Claim 8 (Original): A method of promoting the production of a neurotrophic factor, which comprises administering an effective amount of N-acetyl-L-pipecolic acid or a pharmaceutically acceptable salt thereof.

Claim 9 (New): The method of claim 7, wherein said neurodegenerative disease is Alzheimer's disease, Parkinson's disease, spinal injury, Huntington's disease, cerebral infarction, head trauma, multiple sclerosis, amyotrophic lateral sclerosis, or diabetic or drug-induced peripheral neuropathy or retinal neuropathy.

Claim 10 (New): The method of claim 8, wherein said neurotrophic factor is neurotrophin.

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=> d his ful l21-

     FILE 'REGISTRY' ENTERED AT 19:25:47 ON 16 JUN 2006
L21            1 SEA ABB=ON  PLU=ON  "N-ACETYL-L-PIPECOLIC ACID"/CN

     FILE 'HCAPLUS' ENTERED AT 19:31:52 ON 16 JUN 2006

     FILE 'REGISTRY' ENTERED AT 19:31:52 ON 16 JUN 2006
                SET SMARTSELECT ON
L22             SEL PLU=ON  L21 1- CHEM :       3 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 19:32:37 ON 16 JUN 2006
L23            6 SEA ABB=ON  PLU=ON  L22
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L24          382 SEA ABB=ON  PLU=ON  PIPECOLIC

     FILE 'HCAPLUS' ENTERED AT 19:34:26 ON 16 JUN 2006
L25         4330 SEA ABB=ON  PLU=ON  L24 OR PIPECOL?

     FILE 'REGISTRY' ENTERED AT 19:35:44 ON 16 JUN 2006
L26          383 SEA ABB=ON  PLU=ON  NEUROTROPHIN?

     FILE 'HCAPLUS' ENTERED AT 19:36:24 ON 16 JUN 2006
L27        12485 SEA ABB=ON  PLU=ON  L26 OR ?NEUROTROPHIN? OR NEUROTROPHIC
                FACTOR?/CV
L28           23 SEA ABB=ON  PLU=ON  L25 AND L27
L29       137170 SEA ABB=ON  PLU=ON  NEURODEGENERAT?/CV OR ALZHEIMER?/CV OR
                PARKINSON?/CV OR (HEAD OR SPINAL)(2A)(TRAUMA OR INJUR?) OR
                HUNTINGTON?/CV OR CEREBRAL INFARCTION? OR MULTIPLE SCLEROSIS?/C
                V OR  AMYOTROPH?/CV OR ALS OR DIABET?/CV OR NEUROPATH?/CV
L30       465718 SEA ABB=ON  PLU=ON  "NERVE, DISEASE"/CV OR NERVE(2A)DISEASE OR
                ?NEURODEG? OR ?ALZHEIMER? OR ?PARKINS? OR ?HUNTINGTON? OR
                ?INFARCT? OR ?SCLEROSIS? OR ?DIABET? OR ?NEUROPATH? OR ?SENIL?
                OR ?DEMENTI? OR MEMORY
L32           55 SEA ABB=ON  PLU=ON  L25(L)(L29 OR L30)
L33         4154 SEA ABB=ON  PLU=ON  L25 AND PD=<NOVEMBER 10, 2004
L35           68 SEA ABB=ON  PLU=ON  (L32 OR L28) NOT L23
L36           62 SEA ABB=ON  PLU=ON  L33 AND L35
                D STAT QUE L36
                D IBIB ABS HITSTR L36 1-62
L37          374 SEA ABB=ON  PLU=ON  "FURUKAWA SHOEI"/AU OR FURUKAWA S/AU
L38          121 SEA ABB=ON  PLU=ON  "NITTA ATSUMI"/AU OR NITTA A/AU
L39           36 SEA ABB=ON  PLU=ON  (L37 AND L38) NOT (L23 OR L36)
L40            0 SEA ABB=ON  PLU=ON  ((L37 OR L38) AND L25) NOT (L23 OR L36)
                D STAT QUE L39
                D IBIB ABS HITSTR L39 1-36
                D STAT QUE L40


     FILE HCAPLUS

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     for records published or updated in Chemical Abstracts after December
     26, 1996), unless otherwise indicated in the original publications.
     The CA Lexicon is the copyrighted intellectual property of the
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FILE COVERS 1907 - 16 Jun 2006 VOL 144 ISS 26
FILE LAST UPDATED: 15 Jun 2006 (20060615/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 15 JUN 2006 HIGHEST RN 887970-41-4
DICTIONARY FILE UPDATES: 15 JUN 2006 HIGHEST RN 887970-41-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 19:32:37 ON 16 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 16 Jun 2006  VOL 144 ISS 26
FILE LAST UPDATED: 15 Jun 2006  (20060615/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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=>

=> d stat que l23
L21           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "N-ACETYL-L-PIPECOLIC
                ACID"/CN
L22             SEL  PLU=ON  L21 1- CHEM :       3 TERMS
L23           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22


=> d ibib abs hitstr l23 1-6

L23  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:354793  HCAPLUS
DOCUMENT NUMBER:          140:350604
TITLE:                    Neurotrophic factor production promoter
INVENTOR(S):              Furukawa, Shoei; Nitta, Atsumi
PATENT ASSIGNEE(S):       Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE:                   PCT Int. Appl., 25 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2004035053         A1    20040429    WO 2003-JP13099         20031010
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,
             PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
             TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

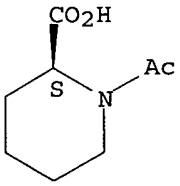
CA 2500417	AA	20040429	CA 2003-2500417	20031010
AU 2003272985	A1	20040504	AU 2003-272985	20031010
EP 1552834	A1	20050713	EP 2003-754096	20031010
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005282865	A1	20051222	US 2005-529784	20050330
PRIORITY APPLN. INFO.:			JP 2002-300247 A	20021015
			WO 2003-JP13099 W	20031010

AB It is intended to provide a neurotrophic factor production promoter which contains, as the active ingredient, N-acetyl-L-pipecolinic acid or its pharmaceutically acceptable salt and is usable in preventing or treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, spinal injury, Huntington's disease, brain infarction, cranial trauma, multiple sclerosis, amyotrophic lateral sclerosis, diabetic or drug-induced peripheral neuropathy and retinal neuropathy.

IT **111555-81-8 111555-81-8D**, salts
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-acetyl-L-pipecolinic acid or its pharmaceutically acceptable salts as neurotrophic factor production promoters for treatment of nervous system diseases)

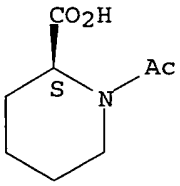
RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:535126 HCAPLUS
DOCUMENT NUMBER: 133:150919
TITLE: Preparation of peptidyl heterocyclic ketones useful as tryptase inhibitors

INVENTOR(S): Costanzo, Michael J.; Maryanoff, Bruce E.; Yabut, Stephen C.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000044733	A1	20000803	WO 2000-US883		20000113
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2361479	AA	20000803	CA 2000-2361479		20000113
EP 1147097	A1	20011024	EP 2000-909902		20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200102766	T2	20011221	TR 2001-2766		20000113
BR 2000007778	A	20020604	BR 2000-7778		20000113
EE 200100391	A	20021015	EE 2001-391		20000113
JP 2002535394	T2	20021022	JP 2000-595989		20000113
US 6469036	B1	20021022	US 2000-482802		20000113
TW 229669	B1	20050321	TW 2000-89101335		20000224
NO 2001003666	A	20010926	NO 2001-3666		20010726
BG 105762	A	20020329	BG 2001-105762		20010801
HR 2001000601	A1	20020831	HR 2001-601		20010813
ZA 2001006995	A	20021125	ZA 2001-6995		20010823
US 2003008829	A1	20030109	US 2002-205355		20020725
PRIORITY APPLN. INFO.:			US 1999-117602P	P	19990127
			US 2000-482802	A3	20000113
			WO 2000-US883	W	20000113

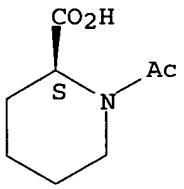
OTHER SOURCE(S): MARPAT 133:150919

AB Peptidyl heterocyclic ketones A-NRCR1R2CO-E [A = substituted cycloalkylcarbonyl, norbornanecarbonyl, norbornenecarbonyl, adamantanecarbonyl, arylcarbonyl, heteroarylcarbonyl, aminoalkylcarbonyl, an amino acid or dipeptide residue, etc.; R, R1 = H, alkyl; R2 = amino-, guanidino-, alkylguanidino-, dialkylguanidino-, amidino-, alkylamidino-, dialkylamidino-, or alkoxyalkyl, (un)substituted Ph, benzyl, pyridyl, pyridyl-, pyrimidyl-, triazinyl-, or imidazoalkyl, imidazolinyl-, N-amidinopiperazinyl-, hydroxy-, alkylamino-, dialkylamino-, N-amidinopiperidinyl-, or 4-aminocyclohexylalkyl; E = (un)substituted heterocyclyl] and their pharmaceutically acceptable salts and prodrugs were prepared as tryptase inhibitors and are therefore effective for the prevention and treatment of inflammatory diseases associated with the respiratory tract, such as asthma and allergic rhinitis. Thus, (2S,4R)-1-acetyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(2-benzothiazolylcarbonyl)butyl]-4-hydroxy-2-pyrrolidinecarboxamide was prepared by a seven-step procedure starting from Boc-Arg(Ts)-OH (Boc, tert-butoxycarbonyl, Ts = tosyl), benzothiazole, and trans-1-acetyl-4-benzyloxyl-L-proline and showed IC50 = 0.036 ± 0.031 μM for inhibition of tryptase.

IT **111555-81-8**

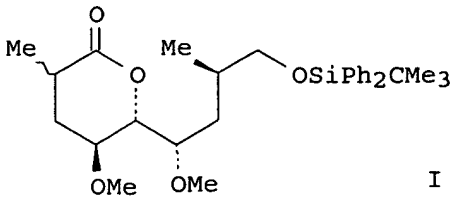
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptidyl heterocyclic ketones useful as tryptase inhibitors)
RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:50007 HCAPLUS
DOCUMENT NUMBER: 128:127838
TITLE: Synthetic studies on the immunosuppressive agent FK-506: construction of the polycarbonyl region
AUTHOR(S): Rupprecht, Kathleen M.; Baker, Robert K.; Boger, Joshua; Davis, Alita A.; Hodges, Paul J.; Kinneary, Joanne F.
CORPORATE SOURCE: Merck Research Laboratories, Department of Medicinal Chemistry, Rahway, NJ, 07065-0900, USA
SOURCE: Tetrahedron Letters (1998), 39(3/4), 233-236
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 128:127838
GI



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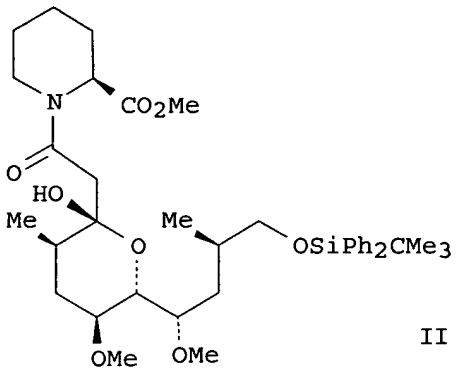


II

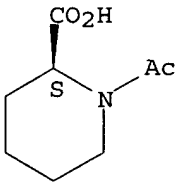
AB The C10-C17 fragment I of the natural product, FK-506, has been stereoselectively synthesized from L-gulose. Methods for elaboration to the C1-C17 fragment II and installation of the C9 carbonyl group are described.

IT **111555-81-8, N-Acetyl-L-pipecolic acid**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective synthesis of the polycarbonyl region of FK-506 from L-gulose)

RN 111555-81-8 HCAPLUS

CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:140700 HCAPLUS

DOCUMENT NUMBER: 126:131280

TITLE: A Unified Total Synthesis of the Immunomodulators (-)-Rapamycin and (-)-27-Demethoxyrapamycin: Assembly of the Common C(1-20) Perimeter and Final Elaboration

AUTHOR(S): Smith, Amos B., III; Condon, Stephen M.; McCauley, John A.; Leazer, Johnnie L., Jr.; Leahy, James W.;

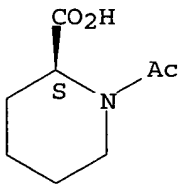
Maleczka, Robert E.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Journal of the American Chemical Society (1997), 119(5), 962-973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:131280

AB The potent, naturally occurring immunomodulators (-)-rapamycin and (-)-27-demethoxy-rapamycin were synthesized via a unified and highly convergent strategy. Model studies of triene generation and hydroxyl deprotection, the preparation and coupling of building blocks D and E, a two-step protocol for macrocycle formation via union of the ABC and DE subtargets, and completion of the total syntheses were described. The synthesis of 27-demethoxyrapamycin confirmed the assigned structure.

IT **111555-81-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(total synthesis of the immunomodulators (-)-rapamycin and (-)-27-demethoxyrapamycin)

RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:554018 HCAPLUS
DOCUMENT NUMBER: 123:55541
TITLE: Total Synthesis of Rapamycin and Demethoxyrapamycin
AUTHOR(S): Smith, Amos B., III; Condon, Stephen M.; McCauley, John A.; Leazer, Johnnie L., Jr.; Leahy, James W.; Maleczka, Robert E., Jr.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Journal of the American Chemical Society (1995), 117(19), 5407-8
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 123:55541

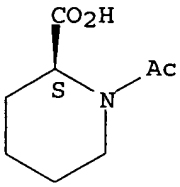
AB Total syntheses of the potent immunomodulators rapamycin and demethoxyrapamycin (I) have been achieved via a highly convergent strategy. The construction of I, achieved for the first time, also served to confirm its assigned structure. Final assembly of the targets entailed coupling of fully functionalized fragments followed by Stille macrocyclization. For rapamycin, the longest linear sequence from the

first point of convergence is fourteen steps.

IT **111555-81-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(total synthesis of rapamycin and demethoxyrapamycin)

RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



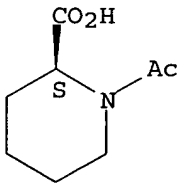
L23 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:32885 HCAPLUS
Correction of: 1988:469870
DOCUMENT NUMBER: 112:32885
Correction of: 109:69870
TITLE: Enzymes in organic synthesis. 40. Evaluation of the enantioselectivity of the pig liver esterase-catalyzed hydrolyses of racemic piperidine carboxylic acid esters
AUTHOR(S): Toone, Eric J.; Jones, J. Bryan
CORPORATE SOURCE: Dep. Chem., Univ. Toronto, Toronto, ON, M5S 1A1, Can.
SOURCE: Canadian Journal of Chemistry (1987), 65(12), 2722-6
CODEN: CJCHAG; ISSN: 0008-4042
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:32885

AB Pig liver esterase-catalyzed hydrolysis of racemic piperidine esters proceeds enantioselectively to give product acids and recovered esters in 0-47% enantiomeric excess.

IT **111555-81-8P**
RL: PREP (Preparation)
(preparation of, from racemic esters with pig liver esterase)

RN 111555-81-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-acetyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



=> => d stat que l36
L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON "N-ACETYL-L-PIPECOLIC ACID"/CN

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L22             SEL  PLU=ON  L21 1- CHEM :        3 TERMS
L23           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22
L24         382 SEA FILE=REGISTRY ABB=ON  PLU=ON  PIPECOLIC
L25        4330 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 OR PIPECOL?
L26         383 SEA FILE=REGISTRY ABB=ON  PLU=ON  NEUROTROPHIN?
L27       12485 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 OR ?NEUROTROPHIN? OR
                NEUROTROPHIC FACTOR?/CV
L28          23 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L27
L29      137170 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NEURODEGENERAT?/CV OR
                ALZHEIMER?/CV OR PARKINSON?/CV OR (HEAD OR SPINAL)(2A)(TRAUMA
                OR INJUR?) OR HUNTINGTON?/CV OR CEREBRAL INFARCTION? OR
                MULTIPLE SCLEROSIS?/CV OR  AMYOTROPH?/CV OR ALS OR DIABET?/CV
                OR NEUROPATH?/CV
L30      465718 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "NERVE, DISEASE"/CV OR
                NERVE(2A)DISEASE OR ?NEURODEG? OR ?ALZHEIMER? OR ?PARKINS? OR
                ?HUNTINGTON? OR ?INFARCT? OR ?SCLEROSIS? OR ?DIABET? OR
                ?NEUROPATH? OR ?SENIL? OR ?DEMENTI? OR MEMORY
L32          55 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25(L)(L29 OR L30)
L33        4154 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND PD=<NOVEMBER 10, 2004

L35          68 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L32 OR L28) NOT L23
L36          62 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L35


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=>

=> d ibib abs hitstr l36 1-62

L36  ANSWER 1 OF 62  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:978969  HCAPLUS
DOCUMENT NUMBER:          142:18187
TITLE:                    The status, quality, and expansion of the NIH
                          full-length cDNA project: The mammalian gene
                          collection (MGC)
AUTHOR(S):                Gerhard, Daniela S.; Wagner, Lukas; Feingold, Elise
                          A.; Shenmen, Carolyn M.; Grouse, Lynette H.; Schuler,
                          Greg; Klein, Steven L.; Old, Susan; Rasooly, Rebekah;
                          Good, Peter; Guyer, Mark; Peck, Allicon M.; Derge,
                          Jeffery G.; Lipman, David; Collins, Francis S.
CORPORATE SOURCE:         The MGC Project Team, NIH, USA
SOURCE:                   Genome Research (2004), 14(10b), 2121-2127
                          CODEN: GEREFS; ISSN: 1088-9051
PUBLISHER:                Cold Spring Harbor Laboratory Press
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The National Institutes of Health's Mammalian Gene Collection (MGC)
     project was designed to generate and sequence a publicly accessible cDNA
     resource containing a complete open reading frame (ORF) for every human and
     mouse gene.  The project initially used a random strategy to select clones
     from a large number of cDNA libraries from diverse tissues.  Candidate clones
     were chosen based on 5'-EST sequences, and then fully sequenced to high
     accuracy and analyzed by algorithms developed for this project.
     Currently, more than 11,000 human and 10,000 mouse genes are represented
     in MGC by at least one clone with a full ORF.  The random selection
     approach is now reaching a saturation point, and a transition to protocols
     targeted at the missing transcripts is now required to complete the mouse
     and human collections.  Comparison of the sequence of the MGC clones to
     reference genome sequences reveals that most cDNA clones are of very high
     sequence quality, although it is likely that some cDNAs may carry missense
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variants as a consequence of exptl. artifact, such as PCR, cloning, or reverse transcriptase errors. Recently, a rat cDNA component was added to the project, and ongoing frog (Xenopus) and zebrafish (Danio) cDNA projects were expanded to take advantage of the high-throughput MGC pipeline. The sequence data for the full-length clones from this study have been submitted to GenBank/EMBL/DDBJ under accession nos. BC000001-BC077073. [This abstr record is one of 39 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT **480796-39-2 480799-11-9 483241-21-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; status, quality, and expansion of the NIH full-length cDNA project and mammalian gene collection (MGC))
RN 480796-39-2 HCAPLUS
CN Similar to neurotrophin 5 (neurotrophin 4/5) (human clone MGC:21488 IMAGE:3865300) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 480799-11-9 HCAPLUS
CN Similar to cardiotrophin-like cytokine; neurotrophin-1/B-cell stimulating factor-3 (human clone MGC:21195 IMAGE:4453813) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 483241-21-0 HCAPLUS
CN Peroxisomal sarcosine oxidase (mouse strain FVB/N clone MGC:19202 IMAGE:4237443) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **352409-06-4 352845-81-9 355890-02-7**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; status, quality, and expansion of the NIH full-length cDNA project and mammalian gene collection (MGC))
RN 352409-06-4 HCAPLUS
CN DNA (human clone MGC:21488 IMAGE:3865300 Similar to neurotrophin 5 (neurotrophin 4/5) cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 352845-81-9 HCAPLUS
CN DNA (human kidney cardiotrophin 1 cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 355890-02-7 HCAPLUS
CN DNA (mouse strain FVB/N clone MGC:19202 IMAGE:4237443 peroxisomal sarcosine oxidase cDNA plus flanks) (9CI) (CA INDEX NAME)

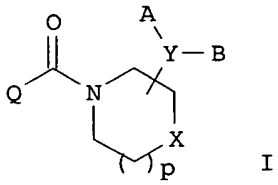
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L36 ANSWER 2 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:308416 HCAPLUS
DOCUMENT NUMBER: 140:339339
TITLE: Preparation of piperidinylcarbonylpiperazines for treatment of neurological diseases
INVENTOR(S): Lauffer, David J.; Botfield, Martyn C.; Eckard, Ottow
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031148	A1	20040415	WO 2003-US31080	20031002 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500672	AA	20040415	CA 2003-2500672	20031002 <--
AU 2003299145	A1	20040423	AU 2003-299145	20031002 <--
US 2004180880	A1	20040916	US 2003-677631	20031002 <--
EP 1546103	A1	20050629	EP 2003-756899	20031002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1717390	A	20060104	CN 2003-80104172	20031002
JP 2006504717	T2	20060209	JP 2004-541991	20031002
NO 2005002153	A	20050531	NO 2005-2153	20050502
PRIORITY APPLN. INFO.:			US 2002-416134P P	20021003
			WO 2003-US31080 W	20031002

OTHER SOURCE(S): MARPAT 140:339339
GI



I

AB Title compds. [I; Q = 3-7 membered (substituted) (unsatd.) N-heterocyclyl; X = C(R2)2, N, NR2, O, S, SO, SO2; Y = bond, O, (O-, S-, SO-, SO2-, CO-, imino-interrupted) alkyl, alkenyl, alkynyl; p = 0-2; A, B = null, H, (substituted) (hetero)aryl; R2 = H, alkyl, alkenyl, alkynyl], were prepared Thus, pivaloyl chloride was added dropwise to (S)-1-tert-butoxycarbonyl-2-piperidinecarboxylic acid and Et3N in CH2Cl2 over 1 h followed by stirring for 2 h; 1-[bis(3,4-difluorophenyl)methyl]piperazine (preparation given) in CH2Cl2 was added over 2 h followed by stirring overnight to give 80% 2-[4-[bis(3,4-difluorophenyl)methyl]piperazine-1-carbonyl]piperidine-1-carboxylic acid tert-Bu ester. The latter was treated with CF3CO2H in CH2Cl2 to give [4-[bis(3,4-difluorophenyl)methyl]piperazin-1-yl]piperidin-2-ylmethanone. The latter inhibited NMDA-induced neuroexcitotoxic injury to rat embryo mesencephalic cell suspensions with IC50 = 6 nM.

IT **130939-66-1**, **Neurotrophin**-3 **143375-33-1**, **Neurotrophin** 4/5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of piperidinylcarbonylpiperazines for treatment of neurol. diseases)

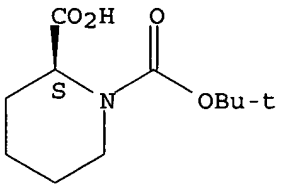
RN 130939-66-1 HCAPLUS

CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 143375-33-1 HCAPLUS
CN Neurotrophin 4/5 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **26250-84-0**, (S)-1-tert-Butoxycarbonyl-2-piperidinecarboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of piperidinylcarbonylpiperazines for treatment of neurol. diseases)
RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

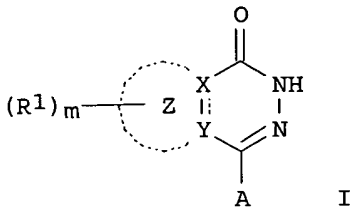
L36 ANSWER 3 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:678790 HCAPLUS
DOCUMENT NUMBER: 139:214477
TITLE: Preparation of fused pyridazine derivatives as poly(ADP-ribose)polymerase inhibitors
INVENTOR(S): Seko, Takuya; Takeuchi, Jun; Takahashi, Shinya; Kamanaka, Yoshihisa; Kamoshima, Wataru
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 368 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070707	A1	20030828	WO 2003-JP1694	20030218 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2476406	AA	20030828	CA 2003-2476406	20030218 <--
AU 2003211381	A1	20030909	AU 2003-211381	20030218 <--
EP 1477175	A1	20041117	EP 2003-705265	20030218

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK						
BR 2003007780	A	20041228	BR 2003-7780			20030218
US 2005085476	A1	20050421	US 2003-505012			20030218
CN 1646499	A	20050727	CN 2003-808459			20030218
ZA 2004006507	A	20050221	ZA 2004-6507			20040816
NO 2004003429	A	20041119	NO 2004-3429			20040817
PRIORITY APPLN. INFO.:			JP 2002-42259	A		20020219
			JP 2002-199673	A		20020709
			WO 2003-JP1694	W		20030218

OTHER SOURCE(S): MARPAT 139:214477

GI



I

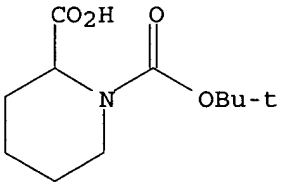
AB The title compds. (I) and pharmaceutically acceptable salts thereof [R1 = H, C1-8 alkyl, C1-8 alkoxy, HO, halo, NO2, each optionally N-mono- or dialkylated NH2 or amino-C2-8 acyl, C2-8 acyl, phenyl-C1-8 alkoxy; X, Y = C, CH, N; a solid line accompanied by a dotted line is a single or double bond; the ring Z containing X and Y = each partially or completely saturated C3-10 monocyclic carbocyclic aryl or 3- to 10-membered monocyclic heterocyclic aryl containing 1-4 heteroatoms selected from O, N, and S; A = Q, Q1, Q2, Q3, etc.; wherein D1 = each N-(un)substituted NHCO, NHC(S), NHSO2, CH2NH, CH2NHCO, NHCONH, NH, NHCO2, NHC(S)NH, NH, or NHC(:NH), CH2O, OC(O); D2 = C1-8 alkylene, C2-8 alkenylene, Cyc2, -(C1-4 alkylene)-O-(C1-4 alkylene)-, -(C1-4 alkylene)-S-(C1-4 alkylene)-, -(C1-4 alkylene)-NH-(C1-4 alkylene)-, etc.; D3 = H, Cyc3, each (un)substituted NH2, CONH2, C(:CH)NH2, or NHC(:NH)NH2, OH, alkoxy, CO2H, alkoxycarbonyl, cyano, halo; G1 = C1-8 alkylene; G2 = H, C1-8 alkyl, C1-8 alkoxy, C2-8 acyl, Cyc6, NO2, Cyc6-C1-8 alkoxycarbonyl, -CO-Cyc6, etc.; R5 = H, C1-8 alkyl, C1-8 alkoxy, HO,NO2, each N-(un)substituted NH2 or amino-C1-8 alkyl, NHSO2OH, amidino, etc.; Cyc1, Cyc2, Cyc3, Cyc5, Cyc6 = groups each partially or completely saturated and monocyclic or bicyclic C3-10 carbocyclic aryl or 3- to 10-membered heterocyclic aryl containing 1-4 heteroatoms selected from O, N, and S] are prepared Because of inhibiting poly(ADP-ribose)polymerase, the compds. I are useful as preventives and/or remedies for various ischemic diseases (in brain, cord, heart, digestive tract, skeletal muscle, retina, etc.), inflammatory diseases (inflammatory bowel disease, multiple cerebrosclerosis, arthritis, etc.), neurodegenerative diseases (extrapyramidal disorder, Alzheimer's disease, muscular dystrophy, lumbar spinal canal stenosis, etc.), cataract, diabetes, diabetes complications, shock, head trauma, spinal cord injury, renal failure, and hyperalgesia. Moreover, these compds. are useful as agents against retroviruses (HIV, etc.) and sensitizers in treating cancer and immunosuppressants. Thus, a solution of 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride in THF (1 M, 20.0 mL) was added to a solution of 3.04 g 3,4,5,6-tetrahydrophthalic anhydride in 40.0 mL THF at -78°, stirred for 1.5 h, treated with

saturated aqueous NH4Cl solution, stirred at room temperature for 30 min to give, after workup, 3-(3-aminophenyl)-3-hydroxy-4,5,6,7-tetrahydro-2-benzofuran-1(3H)-one (II) as an oil. SOCl2 (5.20 mL) was added dropwise to 20.0 mL MeOH at -10°, stirred at 0° for 15 min, treated with II, stirred at room temperature for 18 h, concentrated, dissolved in 20 mL CH2Cl2, treated with Et3N, treated with H2O, and extracted with CH2Cl2 to give, after workup and silica gel chromatog., 3-(3-aminophenyl)-3-methoxy-4,5,6,7-tetrahydro-2-benzofuran-1(3H)-one (III). A solution of 2.56 g III and 503 mg hydrazine monohydrate in 30.0 mL EtOH was refluxed for 18 h, cooled to room temperature, and filtered to give, after washing the crystals obtained with hexane and drying, 32.0 mg 4-(3-aminophenyl)-5,6,7,8-tetrahydrophthalazine-1(2H)-one. 4-(3,5-Diaminophenyl)-6,7,9,9a-tetrahydro[1,4]thiazino[4,3-d][1,2,4]triazin-1(2H)-one, 8-(3-aminophenyl)-2,3,4,6-tetrahydropyrido[2,3-d]pyridazin-5(1H)-one mono- or dihydrochloride, and 4-[N-(2-aminoethyl)carbamoylmethyl]-5,6,7,8-tetrahydrophthalazin-1(2H)-one (IV) showed IC50 of 0.61, 0.10, and 0.29 μg/mL, resp. against poly(ADP-ribose)polymerase. A tablet and an ampule formulation containing IV were described.

IT **98303-20-9**, 1-tert-Butoxycarbonylpiperidine-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of fused pyridazine derivs. as poly(ADP-ribose)polymerase inhibitors for treatment or prevention of diseases such as ischemia, inflammations and **neurodegenerative** diseases)

RN 98303-20-9 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:542070 HCAPLUS

DOCUMENT NUMBER: 140:3610

TITLE: **Pipecolic** acid induces apoptosis in neuronal cells

AUTHOR(S): Matsumoto, Shinji; Yamamoto, Satoshi; Sai, Katsunari; Maruo, Keishi; Adachi, Masaru; Saitoh, Masaru; Nishizaki, Tomoyuki

CORPORATE SOURCE: Department of Physiology, Hyogo College of Medicine, Nishinomiya, 663-8501, Japan

SOURCE: Brain Research (**2003**), 980(2), 179-184
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

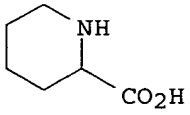
LANGUAGE: English

AB **Pipecolic** acid, a lysine metabolite, is thought to be a factor responsible for hepatic encephalopathy; however, the underlying mechanism is far from understood. Twenty minutes treatment with d-, l-, and dL-

pipecolic acid at concns. ranging from 1 to 100 μM, except for 1 μM l- **pipecolic** acid, had no inhibitory effect on excitatory postsynaptic responses in the dentate gyrus of rat hippocampal slices. In a whole-cell voltage-clamp configuration, dL-**pipecolic** acid (10 and 100 μM) did not affect voltage-sensitive Na+ channel currents and K+ channel currents, but it potentiated voltage-sensitive Ca2+ channel currents, but to a lesser extent, in cultured rat cortical neurons and Neuro-2A cells, a mouse neuroblastoma cell line. Notably, 72-h treatment with d-, l-, and dL-**pipecolic** acid reduced Neuro-2A cell viability in a dose-dependent manner at concns. ranging from 1 to 100 μM in a 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, in parallel with reactions to propidium iodide, a marker of cell death, and Hoechst 33342, a marker of apoptosis in a fluorescent microscopic study, with dL-**pipecolic** acid being the most potent. The results of the present study suggest that **pipecolic** acid could cause hepatic encephalopathy by inducing neuronal cell death, perhaps apoptosis, rather than by depressing neurotransmissions.

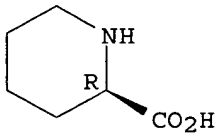
IT **535-75-1**, **Pipecolic** acid **1723-00-8**
3105-95-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**pipecolic** acid induces apoptosis in neuronal cells)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



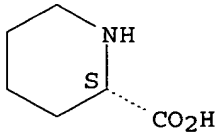
RN 1723-00-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 3105-95-1 HCAPLUS
CN 2-Piperidinecarboxylic acid, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

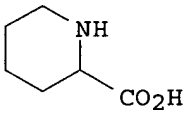
L36 ANSWER 5 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:213281 HCAPLUS
DOCUMENT NUMBER: 139:67295
TITLE: Short Report: Plasma **pipecolic** acid is frequently elevated in non-peroxisomal disease
AUTHOR(S): Baas, J. C. M.; van de Laar, R.; Dorland, L.; Duran, M.; Berger, R.; Poll-The, B. T.; de Koning, T. J.
CORPORATE SOURCE: Department of Metabolic Diseases, University Medical Center Utrecht, Neth.
SOURCE: Journal of Inherited Metabolic Disease (**2002**), 25(8), 699-701
CODEN: JIMDDP; ISSN: 0141-8955
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors reviewed the authors' data on patients in whom plasma **pipecolic** acid was analyzed. Mild to moderate elevations of **pipecolic** acid were frequently found in non-peroxisomal disorders and this should be taken into account when interpreting the laboratory data.

IT **535-75-1**, **Pipecolic** acid
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elevation in plasma **pipecolate** in non-peroxisomal disease)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 6 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:97304 HCAPLUS
DOCUMENT NUMBER: 138:137330
TITLE: Preparation of substituted piperazines as agonists of melanocortin receptors useful against obesity and diabetes
INVENTOR(S): Fotsch, Christopher H.; Arasasingham, Premilla; Bo, Yunxin; Chen, Ning; Goldberg, Martin H.; Han, Nianhe; Hsieh, Feng-Yin; Kelly, Michael G.; Liu, Qingyian; Norman, Mark H.; Smith, Duncan M.; Stec, Markian; Tamayo, Nuria; Xi, Ning; Xu, Shimin
PATENT ASSIGNEE(S): Amgen Inc., USA
SOURCE: PCT Int. Appl., 331 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

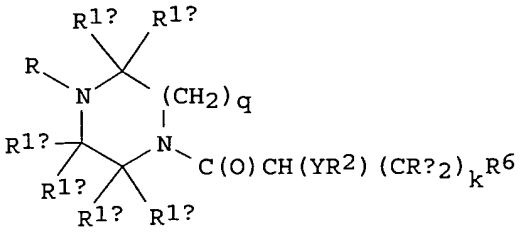
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003009850	A1	20030206	WO 2002-US23926	20020725 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

US 2003220324 A1 20031127 US 2002-202823 20020724 <--
CA 2454903 AA 20030206 CA 2002-2454903 20020725 <--
EP 1417190 A1 20040512 EP 2002-761189 20020725 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
JP 2005503369 T2 20050203 JP 2003-515242 20020725
PRIORITY APPLN. INFO.: US 2001-307831P P 20010725
US 2002-202823 A 20020724
WO 2002-US23926 W 20020725

OTHER SOURCE(S): MARPAT 138:137330
GI



I

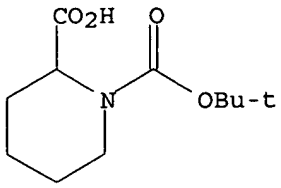
AB Selected substituted piperazine compds. (shown as I; variables defined below; e.g. (3S)-N-[(1S)-1-[(4-chlorophenyl)methyl]-2-[4-[2-[(methylsulfonyl)amino]phenyl]piperazinyl]-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide) are effective for prophylaxis and treatment of diseases, such as obesity and the like. The invention encompasses novel compds., analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compns. and methods for prophylaxis and treatment of diseases and other maladies or conditions involving activation of the melanocortin receptor. The subject invention also relates to processes for making such compds. as well as to intermediates useful in such processes. For I: Y is -NH-, -CH2-, or -O-; R = alkyl, -(CH2)n-cycloalkyl, -(CH2)n-aryl, and -(CH2)n-heterocyclyl; R1a, R1b, R1c, R1d, R1e, and R1f = R4; or R1a and R1b or R1d and R1c form oxo; or wherein R1e and R1c form an alkylenyl or alkenylenyl bridge; or R1a, R1b, R1c, R1d together with the piperazine ring forms an optionally substituted 1,2,3,4-tetrahydroquinoxalinyl ring. R2 = alkyl, -(CH2)n-cycloalkyl, -(CH2)n-aryl, -(CH2)n-heterocyclyl, -SO2R8, -C(O)R8; R4 = H, alkyl, -(CH2)n-cycloalkyl, -(CH2)n-aryl, -(CH2)n-heterocyclyl, halo, -(CH2)n-OR9, -NR9SO2R7, -[C(R7)2]pNR9SO2R7, -[C(R7)2]pNR9C(O)R7, -N(R9)2, -C(O)NR9R9, -NR9C(O)R7, -NR9CO2R7, cyano, -COOR9, -(CH2)n-C:OR7, -(CH2)n-C(S)R7, -(CH2)n-C(:NR9)R7, -NR9C(:NR7)N(R9)2, -[C(R7)2]pN(R9)2, nitro, -SO2N(R9)2, -S(O)mR7, -C(R7)2SO2CF3, hydroxyalkyl, haloalkyl and haloalkoxy. R6 = aryl and heteroaryl; Ra = H, and alkyl or the two Ra's together form cycloalkyl; k is 0 or 1; m is 0, 1 or 2; n is 0, 1, 2, 3 or 4; p is 1 or 2; and q is 1 or 2; provisos and addnl. definitions are provided. In measurements of fast-induced food intake in mice, 6 examples of I caused a reduction in feeding at concns. ≤30 mg/kg. Although the methods of preparation are not claimed, 24 example prepns. of intermediates and

>400 of I are included.

IT **98303-20-9**, Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted piperazines as agonists of melanocortin receptors useful against obesity and **diabetes**)

RN 98303-20-9 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 7 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:55946 HCAPLUS

DOCUMENT NUMBER: 138:84320

TITLE: Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences

AUTHOR(S): Strausberg, Robert L.; Feingold, Elise A.; Grouse, Lynette H.; Derge, Jeffery G.; Klausner, Richard D.; Collins, Francis S.; Wagner, Lukas; Shenmen, Carolyn M.; Schuler, Gregory D.; Altschul, Stephen F.; Zeeberg, Barry; Buetow, Kenneth H.; Schaefer, Carl F.; Bhat, Narayan K.; Hopkins, Ralph F.; Jordan, Heather; Moore, Troy; Max, Steve I.; Wang, Jun; Hsieh, Florence; Diatchenko, Luda; Marusina, Kate; Farmer, Andrew A.; Rubin, Gerald M.; Hong, Ling; Stapleton, Mark; Soares, M. Bento; Bonaldo, Maria F.; Casavant, Tom L.; Scheetz, Todd E.; Brownstein, Michael J.; Usdin, Ted B.; Toshiyuki, Shiraki; Carninci, Piero; Prange, Christa; Raha, Sam S.; Loquellano, Naomi A.; Peters, Garrick J.; Abramson, Rick D.; Mullahy, Sara J.; Bosak, Stephanie A.; McEwan, Paul J.; McKernan, Kevin J.; Malek, Joel A.; Gunaratne, Preethi H.; Richards, Stephen; Worley, Kim C.; Hale, Sarah; Garcia, Angela M.; Gay, Laura J.; Hulyk, Stephen W.; Villalon, Debbie K.; Muzny, Donna M.; Sodergren, Erica J.; Lu, Xiuhua; Gibbs, Richard A.; Fahey, Jessica; Helton, Erin; Ketteman, Mark; Madan, Anuradha; Rodrigues, Stephanie; Sanchez, Amy; Whiting, Michelle; Madan, Anup; Young, Alice C.; Shevchenko, Yuriy; Bouffard, Gerard G.; Blakesley, Robert W.; Touchman, Jeffrey W.; Green, Eric D.; Dickson, Mark C.; Rodriguez, Alex C.; Grimwood, Jane; Schmutz, Jeremy; Myers, Richard M.; Butterfield, Yaron S. N.; Krzywinski, Martin I.; Skalska, Ursula; Smailus, Duane E.; Schnerch, Angelique; Schein, Jacqueline E.; Jones, Steven J. M.; Marra, Marco A.

CORPORATE SOURCE: Mammalian Gene Collection (MGC) Program Team, National Cancer Institute, NIH, Bethesda, MD, 20892-2580, USA

SOURCE: Proceedings of the National Academy of Sciences of the

United States of America (2002), 99(26), 16899-16903
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The National Institutes of Health Mammalian Gene Collection (MGC) Program is a multiinstitutional effort to identify and sequence a cDNA clone containing a complete ORF for each human and mouse gene. ESTs were generated from libraries enriched for full-length cDNAs and analyzed to identify candidate full-ORF clones, which then were sequenced to high accuracy. The MGC has currently sequenced and verified the full ORF for a nonredundant set of >9000 human and >6000 mouse genes. Candidate full-ORF clones for an addnl. 7800 human and 3500 mouse genes also have been identified. All MGC sequences and clones are available without restriction through public databases and clone distribution networks. [This abstract record is one of eleven records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT **480796-39-2 480799-11-9 483241-21-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; generation and initial anal. of more than 15,000 full-length human and mouse cDNA sequences)

RN 480796-39-2 HCAPLUS
CN Similar to neurotrophin 5 (neurotrophin 4/5) (human clone MGC:21488 IMAGE:3865300) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 480799-11-9 HCAPLUS
CN Similar to cardiotrophin-like cytokine; neurotrophin-1/B-cell stimulating factor-3 (human clone MGC:21195 IMAGE:4453813) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 483241-21-0 HCAPLUS
CN Peroxisomal sarcosine oxidase (mouse strain FVB/N clone MGC:19202 IMAGE:4237443) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **352409-06-4 352845-81-9 355890-02-7**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; generation and initial anal. of more than 15,000 full-length human and mouse cDNA sequences)

RN 352409-06-4 HCAPLUS
CN DNA (human clone MGC:21488 IMAGE:3865300 Similar to neurotrophin 5 (neurotrophin 4/5) cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 352845-81-9 HCAPLUS
CN DNA (human kidney cardiotrophin 1 cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 355890-02-7 HCAPLUS
CN DNA (mouse strain FVB/N clone MGC:19202 IMAGE:4237443 peroxisomal sarcosine oxidase cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L36 ANSWER 8 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:22901 HCAPLUS
DOCUMENT NUMBER: 138:66712
TITLE: Peptide structures useful for competitive modulation of dipeptidyl peptidase IV catalysis, and therapeutic use
INVENTOR(S): Demuth, Hans Ulrich; Hoffmann, Torsten; Manhart, Susanne; Hoffmann, Matthias; Heins, Jochen
PATENT ASSIGNEE(S): Probiodrug AG, Germany
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002593	A2	20030109	WO 2002-EP7128	20020627 <--
WO 2003002593	A3	20030904		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003119750	A1	20030626	US 2002-126374	20020419 <--
US 2003130199	A1	20030710	US 2002-172809	20020613 <--
CA 2419888	AA	20030109	CA 2002-2419888	20020627 <--
US 2003135023	A1	20030717	US 2002-186177	20020627 <--
ZA 2003000833	A	20040210	ZA 2003-833	20020627 <--
EP 1399469	A2	20040324	EP 2002-762308	20020627 <--
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ZA 2003001312	A	20040330	ZA 2003-1312	20020627 <--
JP 2004530729	T2	20041007	JP 2003-508973	20020627 <--
ZA 2003000595	A	20040213	ZA 2003-595	20030122 <--
NO 2003000900	A	20030424	NO 2003-900	20030226 <--
US 2005171025	A1	20050804	US 2005-93991	20050330

PRIORITY APPLN. INFO.:		
EP 2001-114796	A	20010627
US 2001-301158P	P	20010627
DE 2001-10150203	A	20011012
DE 2001-10154689	A	20011109
US 2001-340151P	P	20011214
US 2001-340182P	P	20011214
US 2002-360909P	P	20020228
US 2002-172809	A1	20020613
WO 2002-EP7128	W	20020627

OTHER SOURCE(S): MARPAT 138:66712

AB The invention provides compds. ABCDE [A = any amino acid except D-amino acid; B= Pro, Ala, Ser, Gly, Hyp, acetidine-(2)-carboxylic acid, **pipecolic** acid; C = any amino acid except Pro, Hyp, acetidine-(2)-carboxylic acid, **pipecolic** acid, N-alkylated amino acid; D, E = any amino acid or absent] and pharmaceutically acceptable salts thereof. The compds. can be used for the preparation of a medicament for the prophylaxis or treatment of a condition mediated by modulation of dipeptidyl peptidase IV activity, wherein the condition preferably is

selected from impaired glucose tolerance, **diabetes** mellitus, glucosuria and metabolic acidosis.

L36 ANSWER 9 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:927244 HCAPLUS
DOCUMENT NUMBER: 138:11433
TITLE: Method for treating nerve injury caused as a result of surgery
INVENTOR(S): Steiner, Joseph P.; Snyder, Solomon; Burnett, Arthur L.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA; The Johns Hopkins University School of Medicine
SOURCE: PCT Int. Appl., 349 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002096420	A2	20021205	WO 2002-US16806		20020529 <--
WO 2002096420	A3	20030206			
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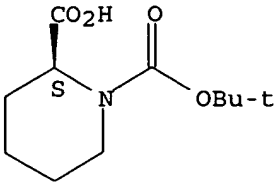
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2449019	AA	20021205	CA 2002-2449019		20020529 <--
US 2003203890	A1	20031030	US 2002-156735		20020529 <--
EP 1404325	A2	20040407	EP 2002-774120		20020529 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2005500270	T2	20050106	JP 2002-592930		20020529
PRIORITY APPLN. INFO.:			US 2001-293544P	P	20010529
			WO 2002-US16806	W	20020529

AB The invention discusses preparation and use of neurotrophic compds. for treating or preventing nerve injury in a warm-blooded animal caused as a consequence of surgery. The invention relates more specifically to methods for treating or preventing nerve injury caused as a consequence of prostate surgery as well as erectile dysfunction.

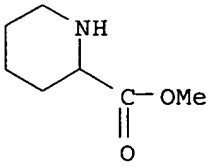
IT **26250-84-0 32559-18-5**, Methyl **pipecolate** hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(neurotrophic agents for treating nerve injury caused as a result of surgery)

RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

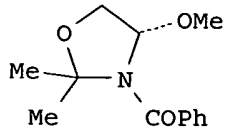


RN 32559-18-5 HCAPLUS
CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L36 ANSWER 10 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:899280 HCAPLUS
DOCUMENT NUMBER: 138:287903
TITLE: Innovative molecular transformations using optically active α-amino acids
AUTHOR(S): Onomura, Osamu
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Nagasaki University, Nagasaki, 852-8521, Japan
SOURCE: Yakugaku Zasshi (**2002**), 122(11), 983-987
CODEN: YKKZAJ; ISSN: 0031-6903
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
GI



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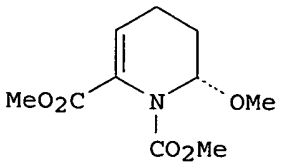

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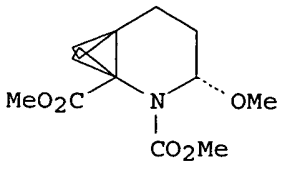

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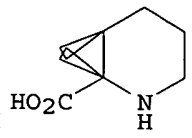

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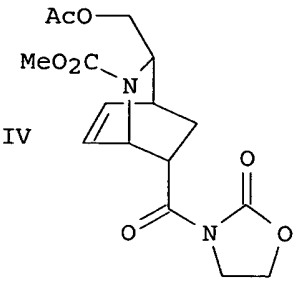

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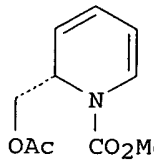

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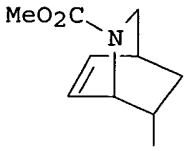

VII

AB A review. Some methods for innovative mol. transformations using optically active α-amino acids have been exploited. (1) The non-Kolbe reaction (electrolytic decarboxy-methoxylation) of the (S)-N-benzoyl-2,2-dimethyloxazolidine-4-carboxylic acid derived from L-serine gave the optically active N,O-acetal (I) when graphite was used an anode material. This reaction represents the first example of " **memory** of chirality" in the carbenium ion chemical (2) The optically active **pipecolic** acid derivative (II), prepared from L-lysine by using electrochem. oxidation, was cyclopropanated with high diastereoselectivity (96.6% de), and the product (III) was transformed into (2S,3R)-2,3-methanopipecolic acid (IV). (3) An enantiomerically pure 1,2-dihydropyridine (V) was prepared from L-lysine using electrochem. oxidation as a key step and was utilized as a chiral diene synthon in the Diels-Alder reaction. That is, in the presence of AlCl3, the Diels-Alder reaction between V and N-acryloyloxazolidin-2-one gave a cycloadduct (VI) with high stereoselectivity, which was converted to an optically active isoquinuclidine derivative (VII) (96.8% ee). (4) The Hofmann rearrangement of N-tert-butoxycarbonyl-L-glutamine Me ester to the enantiomerically pure (S)-4-[(2,2,2-trifluoroethoxycarbonyl)amino]-2-(tert-butoxycarbonylamino)butyric acid Me ester was successfully achieved with an electrochem. method using a trifluoroethanol-MeCN solvent system. (5) Some types of N-formyl cyclic amine derivs. were found to be effective activators of trichlorosilane to reduce ketones and imines. Namely, the reduction of ketones and imines by trichlorosilane with a catalytic amount of Nα-formyl-N-(1-naphthyl)-L-prolinamide and Nα-formyl-N-phenyl-L-prolinamide gave enantiomerically enriched sec-alcs. and amines, resp. to some extent of optical yields.

L36 ANSWER 11 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:849596 HCAPLUS
DOCUMENT NUMBER: 137:370353
TITLE: Preparation of spiropiperidine derivatives, nociceptin receptor antagonists containing the same as the active

ingredient, and medicinal compositions

INVENTOR(S): Sagara, Takeshi; Itoh, Satoru; Nakashima, Hiroshi; Goto, Yasuhiro; Shimizu, Atsushi; Iwasawa, Yoshikazu; Okamoto, Osamu

PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088089	A1	20021107	WO 2002-JP3878	20020418 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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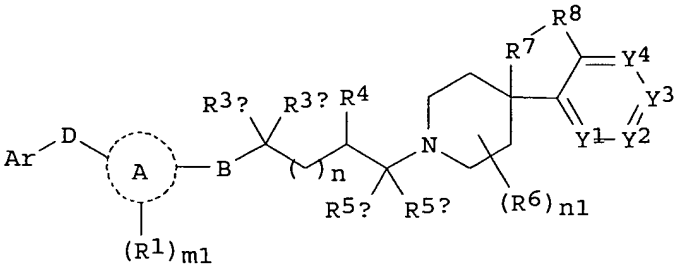
PRIORITY APPLN. INFO.: JP 2001-121543 A 20010419
OTHER SOURCE(S): MARPAT 137:370353

GI



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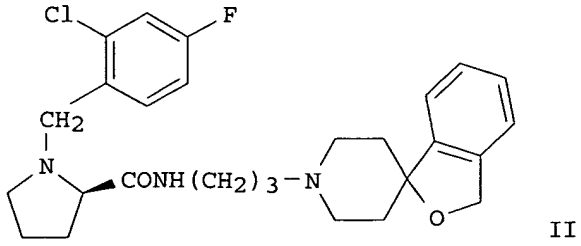


II

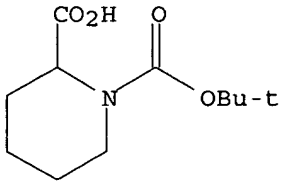
AB Spiropiperidine derivs. typified by compds. represented by the general formula (I) or pharmacol. acceptable salts thereof [wherein the ring A = 3- to 6-membered monocyclic aromatic or aliphatic ring optionally containing 1 or ≥2 heteroatoms selected from N, O, and S; B = CONH, NHCO; D = a single bond, O, S, CO, (un)substituted CH2 or CH2CH2; R1 = HO, halo, mono or di(lower alkyl)amino, lower alkylsulfonyl, lower alkylsulfinyl,

optionally F-substituted lower alkoxy, lower alkylcarbonyloxy, lower alkylcarbonylamino, (un)substituted lower alkyl; m1 = an integer of 0-4; n = 0,1; R3a, R3b, R5a, R5b = H, halo, C1-3 alkyl, C1-3 haloalkyl; R4 = H, halo, HO, C1-3 alkyl, C1-3 haloalkyl; or R5a and R5b together form CH2, CH2CH2, or (CH2)3; R6 = halo, C1-3 alkyl; m = an integer of 0-8; R7, R8 = O, CH2; or R7 and R8 together form CH:CH; provided that R7 and R8 are not simultaneously O; Ar = (un)substituted mono- or bicyclic aryl or heteroaryl; Y1-Y4 = (un)substituted CH, N; provided that ≥2 of Y1-Y4 are not simultaneously N]. These compds. have an antagonistic effect on the binding of nociceptin to a nociceptin receptor ORL1 at an extremely low concentration, which makes them useful as analgesics for cancer pain and diseases in associated with pain, antagonists to narcotic analgesic-tolerance, antagonists to narcotic analgesic -addiction or withdrawal syndrome, analgesic potentiators, antiobesity agents, brain function improving agents, and remedies for Alzheimer's disease, dementia, schizophrenia, Parkinson's disease, Huntington's chorea, depression, diabetes insipidus, polyuria, and hypotension. Thus, to a solution of N-[3-[spiro[isobenzofuran-1(3H),4'-piperidine]-1-yl]propyl]-D-prolinamide dihydrochloride in DMF were added 2-chloro-4-fluorobenzaldehyde and sodium triacetoxyborohydride successively and stirred at room temperature for 4 h to give 1-(2-chloro-4-fluorobenzyl)-N-[3-spiro[isobenzofuran-1(3H),4'-piperidine]-1-ylpropyl]-D-prolinamide (II). II showed IC50 of 0.043 nM for inhibiting the binding of [125I]Tyr14-nociceptin to a membrane preparation obtained from CHO cells transfected with human nociceptin gene.

IT **98303-20-9**, 1-(tert-Butoxycarbonyl)-2-piperidinecarboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of spiropiperidine derivs. as nociceptin receptor antagonists, analgesics, antiobesity agents, brain function improvers, or remedies for **neurodegenerative** diseases, **diabetes** insipidus, polyuria, hypotension, or depression)

RN 98303-20-9 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

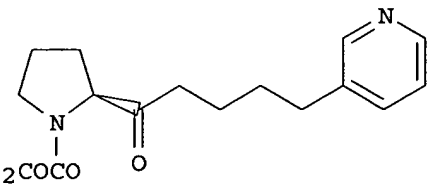
L36 ANSWER 12 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:515544 HCAPLUS
DOCUMENT NUMBER: 137:201562
TITLE: Synthesis of N-Glyoxyl Prolyl and **Pipecolyl** Amides and Thioesters and Evaluation of Their In Vitro and In Vivo Nerve Regenerative Effects
AUTHOR(S): Hamilton, Gregory S.; Wu, Yong-Qian; Limburg, David C.; Wilkinson, Douglas E.; Vaal, Mark J.; Li, Jia-He; Thomas, Christine; Huang, Wei; Sauer, Hansjorg; Ross, Douglas T.; Soni, Raj; Chen, Yi; Guo, Hongshi; Howorth, Pamela; Valentine, Heather; Liang, Shi; Spicer, Dawn; Fuller, Mike; Steiner, Joseph P.
CORPORATE SOURCE: Department of Research, Guilford Pharmaceuticals Inc.,

Baltimore, MD, 21224, USA
SOURCE: Journal of Medicinal Chemistry (**2002**), 45(16), 3549-3557
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:201562

AB The recent discovery that small mol. ligands for the peptidyl-prolyl isomerase (PPIase) FKBP12 possess powerful neuroprotective and neuroregenerative properties in vitro and in vivo suggests therapeutic utility for such compds. in **neurodegenerative** disease. The neurotrophic effects of these compds. are independent of the immunosuppressive pathways by which drugs such as FK506 and rapamycin operate. Previous work by the authors and other groups exploring the structure-activity relationships (SAR) of small mols. that mimic only the FKBP binding domain portion of FK506 has focused on esters of proline and **pipecolic** acid. The authors have explored amide and thioester analogs of these earlier structures and found that they too are extremely potent in promoting recovery of lesioned dopaminergic pathways in a mouse model of **Parkinson**'s disease. Several compds. were shown to be highly effective upon oral administration after lesioning of the dopaminergic pathway, providing further evidence of the potential clin. utility of a variety of structural classes of FKBP12 ligands.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 13 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:511739 HCAPLUS
DOCUMENT NUMBER: 137:216833
TITLE: Synthesis of Ketone Analogues of Prolyl and **Pipecolyl** Ester FKBP12 Ligands
AUTHOR(S): Wu, Yong-Qian; Wilkinson, Douglas E.; Limburg, David; Li, Jia-He; Sauer, Hansjorg; Ross, Doug; Liang, Shi; Spicer, Dawn; Valentine, Heather; Fuller, Mike; Guo, Hong; Howorth, Pam; Soni, Raj; Chen, Yi; Steiner, Joseph P.; Hamilton, Gregory S.
CORPORATE SOURCE: Department of Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Journal of Medicinal Chemistry (**2002**), 45(16), 3558-3568
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:216833
GI



I

AB The recently discovered small-mol. ligands for the peptidyl and prolyl

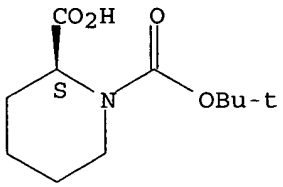
isomerases (PPIase) of FKBP12 have been shown to possess powerful neuroprotective and neuroregenerative effects. Ketone analogs of the prolyl and **pipecolyl** esters, which mimic only the FKBP binding domain portion of FK506, were prepared These compds. are potent neurotrophic agents, potentially useful in treating **neurodegenerative** diseases, such as **Parkinsonism.** The proline derivative I at 0.4-1.0 mg/kg initiated 45% recovery of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced lesions in dopaminergic neurons in vitro.

IT **26250-84-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of ketone analogs of prolyl and **pipecolyl** ester FKBP12 ligands)

RN 26250-84-0 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 14 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:332684 HCAPLUS
DOCUMENT NUMBER: 136:340999
TITLE: Preparation of amino acid derivatives as rotamase enzyme activity inhibitors
INVENTOR(S): Steiner, Joseph P.; Hamilton, Gregory S.
PATENT ASSIGNEE(S): Gpi Nil Holdings, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 359,351.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002052410	A1	20020502	US 2001-805249	20010314 <--
US 7056935	B2	20060606		
US 5614547	A	19970325	US 1995-479436	19950607 <--
US 2002013344	A1	20020131	US 1995-551026	19951031 <--
RU 2269514	C2	20060210	RU 2000-115383	19960605
US 6509477	B1	20030121	US 1999-359351	19990721 <--

PRIORITY APPLN. INFO.:

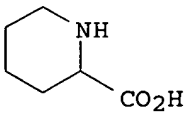
US 1995-479436	A1	19950607
US 1995-551026	A2	19951031
US 1996-693003	B1	19960806
US 1999-359351	A2	19990721
RU 1997-111860	A3	19960605

OTHER SOURCE(S): MARPAT 136:340999

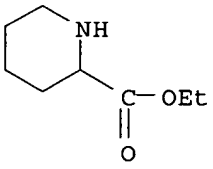
AB The invention relates to methods of using neurotrophic compds. having an affinity for FKBP-type immunophilins to stimulate or promote neuronal growth or regeneration and to prevent neuronal degeneration. Amino acid derivs. R1C(:X)CON(J)CHKCO-Y(CH2)nCHZR2 [n = 0-3; Y is CH2, O, NH, or alkylimino; Z and R2 are independently Ar, or cycloalkyl, cycloalkenyl, or Ar-(un)substituted alkyl or alkenyl, or TCH:C(Q)CH2-, where Q = H, alkyl or alkenyl; T is Ar or substituted cycloalkyl; Ar is an (un)substituted mono or bicyclic heterocyclic aromatic ring; R1 is U, where U is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or cycloalkenyl; X is O or CH-U , provided that if R1 is H, then X is CH-U or if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or cyclohexylethyl; or J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain O, S, SO or SO2] or their pharmaceutically acceptable salts are claimed. Thus, 3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared by esterification of the acid and showed Ki = 0.025 μM for inhibition of rotamase and ED50 = 80 nM for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

IT **535-75-1**, 2-Piperidinecarboxylic acid **15862-72-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of glyoxalylprolinate and -**pipecolinate** derivs. as rotamase inhibitors)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)

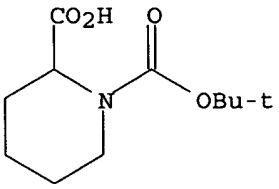


RN 15862-72-3 HCAPLUS
CN 2-Piperidinecarboxylic acid, ethyl ester (9CI) (CA INDEX NAME)



IT **98303-20-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of glyoxalylprolinate and -**pipecolinate** derivs. as rotamase inhibitors)

RN 98303-20-9 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



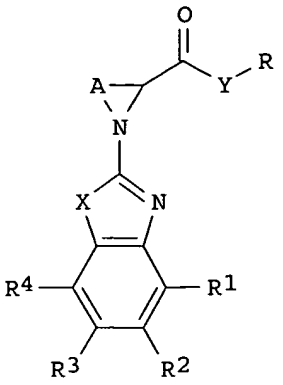
L36 ANSWER 15 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:324910 HCAPLUS
DOCUMENT NUMBER: 137:169758
TITLE: Solid-Phase synthesis of FKBP12 inhibitors: N-Sulfonyl and N-Carbamoylprolyl/**pipecolyl** amides
AUTHOR(S): Wei, Ling; Wu, Yong-Qian; Wilkinson, Douglas E.; Chen, Yi; Soni, Raj; Scott, Chad; Ross, Douglas T.; Guo, Hong; Howorth, Pamela; Valentine, Heather; Liang, Shi; Spicer, Dawn; Fuller, Mike; Steiner, Joseph; Hamilton, Gregory S.
CORPORATE SOURCE: Research Department, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2002**), 12(10), 1429-1433
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:169758
AB In parallel with our work on solution-phase parallel synthesis of ligands for the rotamase enzyme FKBP12, we report a methodol. for the solid-phase synthesis of two classes of inhibitor, N-sulfonyl and N-carbamoylprolyl and **pipecolyl** amides, along with their in vitro/in vivo biol. results. Potent FKBP12 ligands for animal testing have been identified.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 16 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:290791 HCAPLUS
DOCUMENT NUMBER: 136:309922
TITLE: Preparation of benzoxazolyl piperidines and analogs as rotamase enzyme inhibitors
INVENTOR(S): Kemp, Mark Ian; Palmer, Michael John; Sanner, Mark Allen; Wythes, Martin James
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 43 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6372736	B1	20020416	US 1999-358107	19990721 <--
US 6562964	B1	20030513	US 2002-56901	20020123 <--
PRIORITY APPLN. INFO.:			GB 1998-15880 A	19980721
			US 1999-358107 A3	19990721

OTHER SOURCE(S): MARPAT 136:309922

GI



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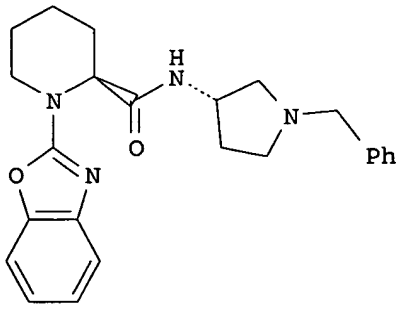


II

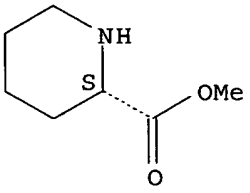
AB Title compds. [I; A = (un)substituted unbranched C3-C5 alkylene; X and Y = independently O, S, NH, or N-alkyl; R = (un)substituted, C-linked, 4- to 6-membered, non-aromatic, heterocyclic ring containing 1 N; R1-R4 = independently H, halo, (cyclo)alkyl, haloalkyl, (cyclo)alkoxy, CONR5R6, cycloalkylalkylene, cycloalkylalkoxy, or CO2R7; R5 and R6 = independently H, alkyl, or taken together = unbranched alkylene; R7 = alkyl] were prepared as rotamase enzyme inhibitors, particularly FKBP-12 and FKBP-52 inhibitors. Thus, (2S)-1-(1,3-benzoxazol-2-yl)-2-piperidinecarboxylic acid (preparation given) was amidated with (3S)-1-benzylpyrrolidine-3-ylamine in the presence of 1-hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.HCl in CH2Cl2 to yield II. Twenty-one compds. of the invention demonstrated inhibitory activity against human recombinant FKBP-12 in a coupled colorimetric PPIase in vitro assay with IC50 values below 1200 nM, and II inhibited the rotamase enzyme FKBP-52 in a similar assay with IC50 = 2790 nM. As neurotrophic agents, the invention compds. promote neuronal regeneration and outgrowth and are useful for the treatment of neurodegenerative diseases or other disorders involving nerve damage.

IT **18650-39-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of benzoxazolyl piperidine derivs. and analogs as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)

RN 18650-39-0 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride, (2S)- (9CI) (CA INDEX NAME)

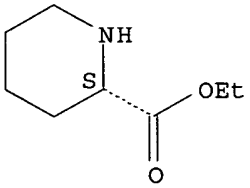
Absolute stereochemistry. Rotation (-).



● HCl

IT **22328-78-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of benzoxazolyl piperidine derivs. and analogs as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)
RN 22328-78-5 HCAPLUS
CN 2-Piperidinecarboxylic acid, ethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 17 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:276521 HCAPLUS
DOCUMENT NUMBER: 136:310178
TITLE: Preparation of amino acid derivatives as rotamase enzyme activity inhibitors
INVENTOR(S): Steiner, Joseph P.; Hamilton, Gregory S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 551,026.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002042377	A1	20020411	US 2001-873298	20010605 <--
US 5614547	A	19970325	US 1995-479436	19950607 <--
US 2002013344	A1	20020131	US 1995-551026	19951031 <--
RU 2269514	C2	20060210	RU 2000-115383	19960605
US 6509477	B1	20030121	US 1999-359351	19990721 <--
PRIORITY APPLN. INFO.:			US 1995-479436 A1	19950607
			US 1995-551026 A2	19951031

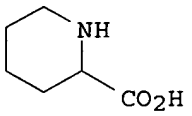
US 1996-693003 B1 19960806
US 1999-359351 A2 19990721
RU 1997-111860 A3 19960605

OTHER SOURCE(S): MARPAT 136:310178

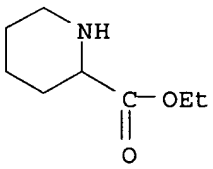
AB The invention relates to methods of using neurotrophic compds. having an affinity for FKBP-type immunophilins to stimulate or promote neuronal growth or regeneration and to prevent neuronal degeneration. Amino acid derivs. R1C(:X)CON(J)CHKCO-Y-Z [Y is O, NH, or alkylimino; Z is H, CHL-Ar, alkyl, alkenyl, cycloalkyl, cycloalkenyl or Ar-substituted alkyl or alkenyl, or TCH:C(Q)CH(L)-, where L and Q are H, alkyl or alkenyl; T is Ar or substituted cyclohexyl; Ar is 1- or 2-naphthyl, 2- or 3-furyl, 2-thienyl, 2-, 3- or 4-pyridyl, (un)substituted phenyl; R1 is U, where U is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or cycloalkenyl; X is O or CH-U , provided that if R1 is H, then X is CH-U or if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or cyclohexylethyl; or J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain O, S, SO or SO2] or their pharmaceutically acceptable salts are claimed. Thus, 3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared by esterification of the acid and showed Ki = 0.025 μM for inhibition of rotamase and ED50 = 80 nM for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

IT **535-75-1**, 2-Piperidinecarboxylic acid **15862-72-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of glyoxalylprolinate and -**pipecolinate** derivs. as rotamase inhibitors)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)

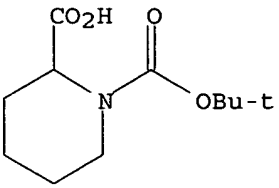


RN 15862-72-3 HCAPLUS
CN 2-Piperidinecarboxylic acid, ethyl ester (9CI) (CA INDEX NAME)



IT **98303-20-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of glyoxalylprolinate and -**pipecolinate** derivs. as rotamase inhibitors)

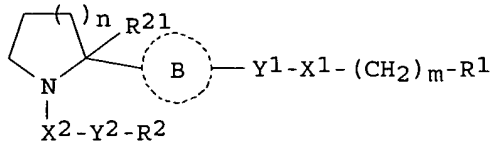
RN 98303-20-9 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



L36 ANSWER 18 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:668212 HCAPLUS
DOCUMENT NUMBER: 135:226999
TITLE: Preparation of 2-azolylpyrrolidine or -piperidine derivatives having neurite outgrowth activity
INVENTOR(S): Kato, Susumu; Ueno, Hiroshi; Kondo, Wataru
PATENT ASSIGNEE(S): Japan Tobacco, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 81 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
JP 2001247569	A2	20010911	JP 2000-236882		20000804	<--
PRIORITY APPLN. INFO.:			JP 1999-228938	A	19990812	
			JP 1999-375867	A	19991228	

OTHER SOURCE(S): MARPAT 135:226999
GI



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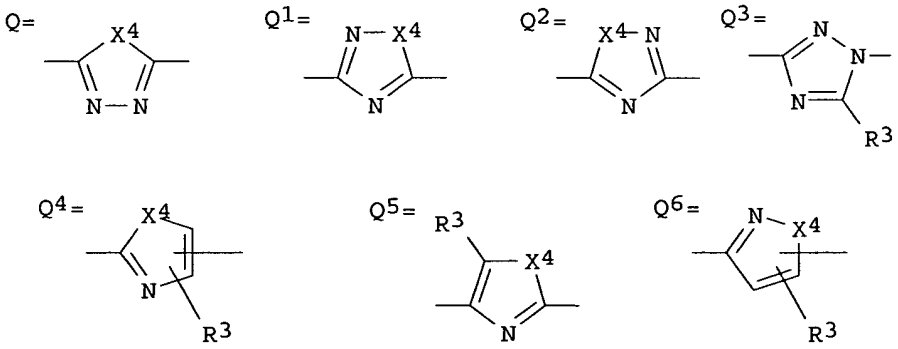
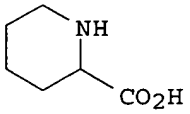


AB The title compds. [I; R1 = H, (un)substituted C3-10 cycloalkyl, C6-12 aryl, or 5- to 6-membered heterocyclyl containing 1-3 heteroatoms selected from O, S, and N; R2 = C1-6 alkyl, C3-10 cycloalkyl, C6-12 aryl, or 5- to 6-membered heterocyclyl containing 1-3 heteroatoms selected from O, S, and N;

R21 = H, C1-6 alkyl; X1 = single bond, O, S, SO, SO2, CH:CH, CO, CO2, NR10, CONR10, NR10CO, NR11CONR10, NR10SO2, SO2NR10, CR10R11 [wherein R10 = H, (CH2)nR12 (wherein n = 1-4; R12 = C3-10 cycloalkyl, C6-12 aryl, or 5- to 6-membered heterocyclyl containing 1-3 heteroatoms selected from O, S, and N); R11 = H, C1-6 alkyl]; Y1 = arylene, heteroarylene, (CH2)p (wherein p = 0, 1-4); X2 = SO2, COCO, CO2, CO, C(S), CONR14, C(S)NR14 (wherein R14 = H, C1-6 alkyl); Y = (CH2)r (wherein r = 0, 1-3), CH:CH; m = 0, 1-4; ring B = Q - Q6 [wherein R3 = H, C1-6 alkyl; X4 = O, S, NR4 (wherein R4 = H, C1-6 alkyl)], (un)substituted condensed heterocyclyl], salts thereof, or their hydrates or prodrugs are prepared These compds. are superior in serum stability and can be administered orally and are useful for the treatment and/or prevention of diseases accompanied by nerve injury or neurodegeneration, e.g. diabetic nerve disorders, neuropathy, nerve cutting, amyotrophic lateral sclerosis (ALC), multiple sclerosis, Alzheimer's diseases, Parkinson's diseases, Huntington chorea, and spinal code injury. Thus, 464 mg 7-chloronaphth-2-ylsulfonyl chloride was added to a solution of 507 mg 5-(5-benzyloxycarbonylaminomethyl-1,3,4-thiadiazol-2-yl)pyrrolidine (preparation given) in pyridine and stirred at room temperature for 3
h to give 706 mg 1-(7-chloronaphthalen-2-ylsulfonyl)-2-(5-benzyloxycarbonylaminomethyl-1,3,4-thiadiazol-2-yl)pyrrolidine which (678 mg) was treated with 25% HBr-AcOH at room temperature for 1 h and treated with diisopropyl ether for precipitating crystals, followed by neutralizing the precipitated
crystals with 1 N aqueous NaOH and extraction with CH2Cl2 to give 472 mg 1-(7-chloronaphthalen-2-ylsulfonyl)-2-(5-aminomethyl-1,3,4-thiadiazol-2-yl)pyrrolidine. To a solution of the latter compound (164 mg) in 2 mL pyridine was added 143 mg nicotinoyl chloride hydrochloride and stirred at room temperature for 30 min to give 183 mg N-[5-[1-(7-chloronaphthalene-2-sulfonyl)pyrrolidin-2-yl]-1,3,4-thiadiazol-2-yl]methyl-3-pyridinecarboxamide (II). II at 10 nM in vitro exhibited the enhancement of the NGF-induced neurite outgrowth in PC12h cells equivalent to that of 100 nM FK-506.

IT **535-75-1**, DL-**Pipecolic** acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 2-azolylpyrrolidine or -piperidine derivs. having neurite outgrowth activity for treatment and/or prevention of nerve injury or **neurodegenerative** diseases)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



L36 ANSWER 19 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:597978 HCAPLUS
DOCUMENT NUMBER: 135:166844
TITLE: Preparation of piperazinyl and piperidinyl ketones useful for treating or preventing neuronal damage and for stimulating nerve growth
INVENTOR(S): Tomlinson, Ronald; Lauffer, David; Mullican, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2001058891	A2	20010816	WO 2001-US4210		20010209	<--
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
CA 2398822	AA	20010816	CA 2001-2398822		20010209	<--
EP 1257544	A2	20021120	EP 2001-912714		20010209	<--
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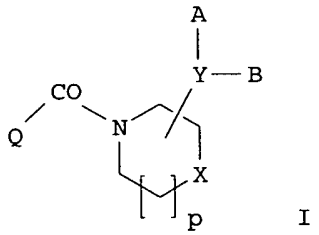
BR 2001008175	A	20030128	BR 2001-8175		20010209	<--
JP 2003522767	T2	20030729	JP 2001-558441		20010209	<--
EE 200200442	A	20031215	EE 2002-442		20010209	<--
NZ 520638	A	20040528	NZ 2001-520638		20010209	<--
ZA 2002005933	A	20030724	ZA 2002-5933		20020724	<--
NO 2002003787	A	20021011	NO 2002-3787		20020809	<--
PRIORITY APPLN. INFO.:			US 2000-181944P	P	20000211	
			US 2000-247330P	P	20001110	
			WO 2001-US4210	W	20010209	

OTHER SOURCE(S): MARPAT 135:166844
GI



I

AB The present invention relates to piperazine and piperidine derivs. I (e.g. 1-[(S)-2-(1,1-diphenylmethyl)pyrrolidin-1-yl]-1-((S)-1-ethylpiperidin-2-yl)methanone), which are especially useful for treating or preventing neuronal damage, particularly damage associated with neurol. diseases. These compds. are also useful for stimulating nerve growth. The invention also provides compns. comprising the compds. of the present invention and methods of using those compns. for treating or preventing neuronal damage or for stimulating nerve growth. In I, each Q is a monocyclic, bicyclic or tricyclic ring system wherein in said ring system: a. each ring is independently partially unsatd. or fully saturated; b. each ring comprises 3 to 7 ring atoms independently = C, N, O or S; c. ≤4 ring atoms in Q are selected from N, O or S; d. any S is optionally replaced with S(O) or S(O)2; e. at least one ring comprises a N ring atom that is substituted with R1; f. 1-5 H atoms in Q are optionally and independently replaced

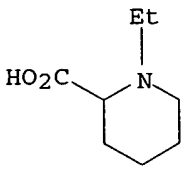
with halo, -OH, :O, :N-OR1, (C1-C6)-straight or branched alkyl, Ar-substituted-(C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, Ar-substituted-(C2-C6)-straight or branched alkenyl or alkynyl, O-(C1-C6)-straight or branched alkyl, O-[(C1-C6)-straight or branched alkyl]-Ar, O-(C2-C6)-straight or branched alkenyl or alkynyl, O-[(C2-C6)-straight or branched alkenyl or alkynyl]-Ar, or O-Ar; and g. Q is not an indole or a pyroglutamic moiety. Each R1 is independently selected from (C1-C6)-straight or branched alkyl, Ar-substituted-(C1-C6)-straight or branched alkyl, cycloalkyl-substituted-(C1-C6) straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar-substituted-(C2-C6)-straight or branched alkenyl or alkynyl. One to two CH2 groups of said alkyl, alkenyl, or alkynyl chains in R1 are optionally and independently replaced with O, S, S(O), S(O)2, C(O) or N(R2), wherein when R1 is bound to N, the CH2 group of R1 bound directly to said N cannot be replaced with C(O). Ar = Ph, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyraxolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, benzoxazolyl, pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, or any other chemical feasible monocyclic or bicyclic ring system, wherein each ring consists of 5 to 7 ring atoms and wherein each ring comprises 0 to 3 heteroatoms independently selected from N, O, or S. Each Ar is optionally and independently substituted with 1-3 substituents selected from halo, hydroxy, nitro, -SO3H, :O, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, O-[(C1-C6)-straight or branched alkyl], O-[(C1-C6)-straight or branched alkenyl], O-benzyl, O-Ph, 1,2-methylenedioxy, -(R3)(R4), carboxy, N-(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) carboxamides, N,N-di(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) carboxamides, N-(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) sulfonamides, or N,N-di(C1-C6-straight or branched alkyl or C2-C6-straight or branched alkenyl) sulfonamides. Each of R3 and R4 = (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, H, Ph or benzyl; or wherein R3 and R4 are taken together with the N atom to which they are bound to form a 5-7 membered heterocyclic ring. Each R2 = H, (C1-C6) straight or branched alkyl, or (C2-C6)-straight or branched alkenyl or alkynyl. X = C(R2)2, N, N(R2), O, S, S(O), or S(O)2. Y = a bond, -O-, (C1-C6)-(straight or branched) alkyl, or (C2-C6)-(straight or branched) alkenyl or alkynyl; wherein Y is bonded to the depicted ring via a single bond or a double bond; and wherein one to two of the CH2 groups of said alkyl, alkenyl, or alkynyl is optionally and independently replaced with O, S, S(O), S(O)2, C(O) or N(R). P = 0-2; each of A and B is independently selected from H or Ar; or one of A or B is absent; and wherein two C ring atoms in the depicted ring structure may be linked to one another via a C1-C4 straight alkyl or a C2-C4 straight alkenyl to create a bicyclic moiety. Results of a neuroprotection assay are tabulated for about 150 of the claimed compds. About 70 example prepns. are included.

IT **130939-66-1**, NT-3 **143375-33-1**, **neurotrophin** 5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined with piperazinyl and piperidinyl ketones useful for treating or preventing neuronal damage and for stimulating nerve growth)

RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 143375-33-1 HCAPLUS
CN Neurotrophin 4/5 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **69081-83-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of piperazinyl and piperidinyl ketones useful for treating or preventing neuronal damage and for stimulating nerve growth)
RN 69081-83-0 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-ethyl- (9CI) (CA INDEX NAME)



L36 ANSWER 20 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:490436 HCAPLUS
DOCUMENT NUMBER: 135:257219
TITLE: Stereoselective synthesis of 1,4-benzodiazepines via photoinduced decarboxylation of N-phthaloylanthranilic acid amides
AUTHOR(S): Griesbeck, Axel G.; Kramer, Wolfgang; Lex, Johann
CORPORATE SOURCE: Institut fur Organische Chemie der Universitat zu Koln, Koln, 50939, Germany
SOURCE: Synthesis (**2001**), (8), 1159-1166
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:257219
AB 5-Chloro-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)benzoic acid and 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)benzoic acid were coupled with a series of amino acids, such as derivs. of sarcosine, alanine, valine, leucine, phenylalanine, aspartic and glutamic acid and several cyclic derivs, of 2-azetidine, **pipecolinic** acid, proline and 2-azabicyclo[3.3.0]undecanoic acid. Also quaternary α-amino acids could be applied as demonstrated for an α-amino isobutyrate derivative Photochem. decarboxylation of amides derived from N-phthaloylanthranilic acid coupled to a series of α-amino acids under basic conditions resulted in 1,4-benzodiazepines. Optically active substrates were converted into non-racemic products with a high degree of chirality **memory** with (inversion of configuration at the stereogenic center) and ee-values of >79%. 4-Chlorinated products were obtained from the 4-chloroanthranilic acid-derived substrates.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 21 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:278023 HCAPLUS

DOCUMENT NUMBER: 134:295745
TITLE: Preparation of heterocyclic thioesters and ketones, and particularly substituted pyrrolidine- and piperidinecarbothioate derivatives, as neurotrophic agents
INVENTOR(S): Hamilton, Gregory S.; Li, Jia-he
PATENT ASSIGNEE(S): GPI NIL Holdings, Inc., USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. 5,990,131.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6218424	B1	20010417	US 1999-444200	19991122 <--
US 5786378	A	19980728	US 1996-721765	19960925 <--
US 5990131	A	19991123	US 1997-904461	19970801 <--
CA 2391575	AA	20010531	CA 2000-2391575	20000830 <--
WO 2001038304	A1	20010531	WO 2000-US23742	20000830 <--
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1233945	A1	20020828	EP 2000-959575	20000830 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003514893	T2	20030422	JP 2001-539860	20000830 <--
AU 784388	B2	20060323	AU 2000-70869	20000830
US 2001056103	A1	20011227	US 2000-733037	20001211 <--
US 6417209	B2	20020709		
US 2002193420	A1	20021219	US 2002-104242	20020325 <--
US 2004106652	A1	20040603	US 2003-615803	20030710 <--
US 6984639	B2	20060110		
US 2005148637	A1	20050707	US 2005-70505	20050303

PRIORITY APPLN. INFO.:		
US 1996-721765	A2	19960925
US 1997-904461	A2	19970801
US 1999-444200	A	19991122
WO 2000-US23742	W	20000830
US 2000-733037	A1	20001211
US 2002-104242	B1	20020325
US 2003-615803	A3	20030710

OTHER SOURCE(S): MARPAT 134:295745
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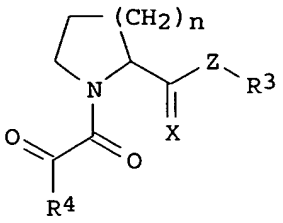

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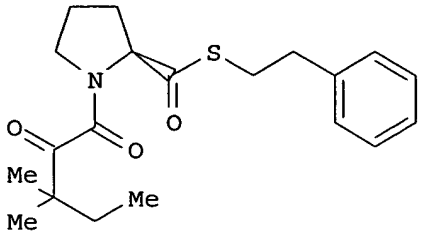


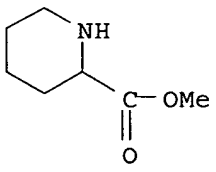
II

AB The invention relates to neurotrophic, low mol. weight, small mol. heterocyclic thioesters and ketones, specifically I [n = 1 or 2; X = O or S; Z = S, CH2, CHR1 and CR1R2; R1-R3 = C1-C5 straight or branched chain alkyl, C2-C5 straight or branched chain alkenyl, or Ar, wherein R1-R3 may be substituted with halo, NO2, C1-C6 straight or branched chain alkyl, C2-C6 straight or branched chain alkenyl, OH, C1-C4 alkoxy, C2-C4 alkenyloxy, PhO, PhCH2O, amino, or Ar; R4 = C1-C9 straight or branched chain alkyl, C2-C9 straight or branched chain alkenyl, C3-C8 cycloalkyl, C5-C7 cycloalkenyl, or Ar; provided that when Z = CH2, R3 = Et, X = O, and n = 2, then R4 ≠ CEtMe2; Ar = (hetero)aryl group having single or multiple condensed rings, wherein Ar may be substituted with halo, OH, NO2, C1-C6 straight or branched chain alkyl, C2-C6 straight or branched chain alkenyl, C1-C4 alkoxy, C2-C4 alkenyloxy, PhO, PhCH2O, or amino] or their pharmaceutically acceptable salts. The compds. have an affinity for FKBP-type immunophilins, and are potent inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl cis-trans isomerase (rotamase) enzyme activity. The compds. may be used to prevent or repair nerve damage, or to prevent the side effects of immunosuppressants. For instance, L-proline Me ester HCl underwent a sequence of: (1) N-acylation with ClCOCOOMe (88%); (2) Grignard reaction with EtMe2CMgCl (75%); (3) ester saponification (87%); and (4) thioesterification with PhCH2CH2SH (84%) to give title compound II. When coadministered at 4 mg/kg s.c. to mice in the MPTP (neurotoxin) model of Parkinson's disease, II gave 61% recovery from lesioning of striatal dopaminergic neurons as determined by tyrosine hydroxylase function.

IT **32559-18-5**, Methyl **pipecolate** hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of substituted pyrrolidine- and piperidinecarbothioate derivs. as neurotrophic agents)

RN 32559-18-5 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



HCl

REFERENCE COUNT: 222 THERE ARE 222 CITED REFERENCES AVAILABLE FOR

THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 22 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:645847 HCAPLUS
DOCUMENT NUMBER: 133:227830
TITLE: Liposome preparations comprising macrolide **pipecolic** acid derivatives
INVENTOR(S): Fujisaki, Jiro; Konno, Hajime; Kasai, Akihiro; Ohtomo, Kazumi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053177	A1	20000914	WO 2000-JP1446	20000310 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2364257	AA	20000914	CA 2000-2364257	20000310 <--
AU 2000029405	A5	20000928	AU 2000-29405	20000310 <--
AU 775694	B2	20040812		
EP 1159962	A1	20011205	EP 2000-907979	20000310 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010459	A	20020205	BR 2000-10459	20000310 <--
TR 200102778	T2	20020521	TR 2001-2778	20000310 <--
NZ 514046	A	20031031	NZ 2000-514046	20000310 <--
ZA 2001007325	A	20021204	ZA 2001-7325	20010904 <--
US 2004028728	A1	20040212	US 2003-636731	20030808 <--
US 6984397	B2	20060110		

PRIORITY APPLN. INFO.:
JP 1999-65469 A 19990311
JP 1999-151866 A 19990531
WO 2000-JP1446 W 20000310
US 2001-926147 B1 20011011

OTHER SOURCE(S): MARPAT 133:227830
AB Disclosed are **pipecolic** acid derivative-containing liposome prepns. which are excellent in the immediate action and thus usable in an urgent situation such as brain **infarction.** These prepns. are characterized by containing **pipecolic** acid derivs. or pharmaceutically acceptable salts thereof, which comprise the components as described in the description, as the active ingredient and lecithin as the major component of lipids forming liposomes, without resort to cholesterol as a stabilizer.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 23 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133663 HCAPLUS
DOCUMENT NUMBER: 132:166133

TITLE: Preparation of hydroxy **pipecolate** hydroxamic acid derivatives as MMP inhibitors

INVENTOR(S): McClure, Kim Francis; Noe, Mark Carl; Letavic, Michael Anthony; Chupak, Louis Stanley

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

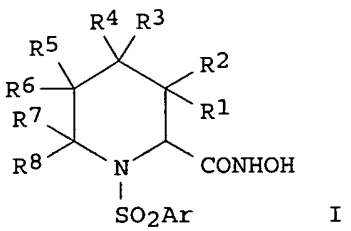
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009485	A1	20000224	WO 1999-IB1388	19990805 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2340202	AA	20000224	CA 1999-2340202	19990805 <--
CA 2340202	C	20060207		
AU 9949247	A1	20000306	AU 1999-49247	19990805 <--
AU 766366	B2	20031016		
BR 9912909	A	20010508	BR 1999-12909	19990805 <--
EP 1104403	A1	20010606	EP 1999-933076	19990805 <--
EP 1104403	B1	20060510		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
TR 200100474	T2	20010621	TR 2001-200100474	19990805 <--
EE 200100086	A	20020815	EE 2001-86	19990805 <--
NZ 509296	A	20031031	NZ 1999-509296	19990805 <--
US 6329397	B1	20011211	US 1999-372946	19990812 <--
ZA 2001001042	A	20021007	ZA 2001-1042	20010207 <--
HR 2001000098	A1	20020228	HR 2001-98	20010208 <--
NO 2001000686	A	20010409	NO 2001-686	20010209 <--
BG 105323	A	20011031	BG 2001-105323	20010309 <--
US 2003008901	A1	20030109	US 2001-8943	20011203 <--

PRIORITY APPLN. INFO.:

US 1998-96232P	P	19980812
WO 1999-IB1388	W	19990805
US 1999-372946	A3	19990812

OTHER SOURCE(S): MARPAT 132:166133

GI



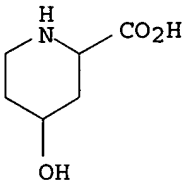
I

AB The title compds. I [R1 - R8 = H, OH, halogen, CN, (un)substituted

(C1-6)alkyl, (un)substituted (C2-6)alkenyl, (un)substituted (C2-10)aryl, (un)substituted (C2-9)heteroaryl, etc; or R1 and R2, or R3 and R4, or R5 and R6 together = carbonyl or form a (C3-6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring; Ar = (un)substituted (C2-10)aryl, (un)substituted (C1-6)alkoxy, (un)substituted (C6-10)aryl, (un)substituted (C2-9)heteroaryl, etc] are prepared Compds. of this invention had IC50 of less than 1 μM in at least one of the assays for inhibiting activities against MMP-1, MMP-2, MMP-3, and MMP-13.

IT **89531-61-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxy **pipecolate** hydroxamic acid derivs. as MMP inhibitors)

RN 89531-61-3 HCAPLUS
CN 2-Piperidinecarboxylic acid, 4-hydroxy-, hydrochloride (9CI) (CA INDEX NAME)



HCl

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 24 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133662 HCAPLUS
DOCUMENT NUMBER: 132:166517
TITLE: **Pipecolic** acid derivatives and related compounds for treatment of vision and **memory** disorders.
INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009484	A1	20000224	WO 1999-US18235	19990812 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6335348	B1	20020101	US 1998-134418		19980814 <--
CA 2340745	AA	20000224	CA 1999-2340745		19990812 <--
AU 9953969	A1	20000306	AU 1999-53969		19990812 <--
EP 1104402	A1	20010606	EP 1999-939730		19990812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002522527	T2	20020723	JP 2000-564938		19990812 <--
PRIORITY APPLN. INFO.:			US 1998-134418	A	19980814
			WO 1999-US18235	W	19990812

OTHER SOURCE(S): MARPAT 132:166517

AB A method for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance comprises administration of LC(:M)CONJCHKCOA(CH2)mCHBD [A = CH2, O, imino; B, D = H, (substituted) Ar, cycloalkylalkyl, cycloalkylalkenyl, arylalkyl, arylalkenyl, etc.; Ar = (substituted) naphthyl, furyl, thienyl, pyridyl, Ph, mono- and bicyclic heterocyclyl; L = H, U; M = O, CHU; U = H, alkoxy, alkenyloxy, alkyl, alkenyl, cycloalkyl cycloalkenylalkyl, etc.; J = H, alkyl, PhCH2; K = alkyl, PhCH2, cyclohexylmethyl; JK = atoms to form a 5-7 membered heterocyclic ring; m = 0-3]. Thus, 3-phenylpropyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate was prepared via solution phase couplings. Tested title compds. inhibited peptidyl prolyl isomerase with Ki = 0.013-80 μM.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 25 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:133657 HCAPLUS

DOCUMENT NUMBER: 132:166121

TITLE: Preparation of heterocyclic thioesters or ketones as FKBP-12 inhibitors for treatment of vision and memory disorders

INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.

PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA

SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

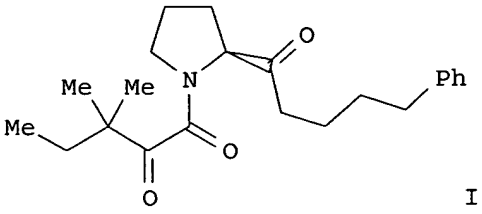
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009479	A2	20000224	WO 1999-US18239	19990812 <--
WO 2000009479	A3	20000518		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6384056	B1	20020507	US 1998-134424	19980814 <--
CA 2340668	AA	20000224	CA 1999-2340668	19990812 <--
AU 9953971	A1	20000306	AU 1999-53971	19990812 <--
EP 1104298	A2	20010606	EP 1999-939732	19990812 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002522525 T2 20020723 JP 2000-564933 19990812 <--
PRIORITY APPLN. INFO.: JP 1998-134424 A 19980814
WO 1999-US18239 W 19990812
OTHER SOURCE(S): MARPAT 132:166121
GI



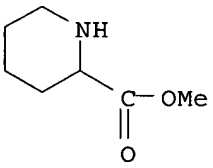
I

AB R2CR3R4CR5R6NR7CHR8C(:X)ZR1 [I; Z = S, CH2, CHR1, CRR1; R,R1 = (un)substituted (ar)alk(en)yl; R2 = (cyclo)alk(en)yl, (hetero)aryl, etc.; R3-R6 = H; R3R4,R5R6 = O, S, CH2; R7R8 = atoms to complete a heterocyclic ring; X = O or S] were prepared Thus, N-benzyl-L-proline was alkylated by ClMg(CH2)4Ph and the deprotected product N-acylated by ClCOCO2Me to give the oxalic pyrrolidide which was alkylated by ClMgCMe2Et to give title compd II. Data for biol. activity of I were given.

IT **32559-18-5**, Methyl **pipecolate** hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heterocyclic thioesters or ketones as FKBP-12 inhibitors for treatment of vision and **memory** disorders)

RN 32559-18-5 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

L36 ANSWER 26 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133482 HCAPLUS
DOCUMENT NUMBER: 132:175851
TITLE: **Pipecolic** acid derivatives for vision and **memory** disorders
INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

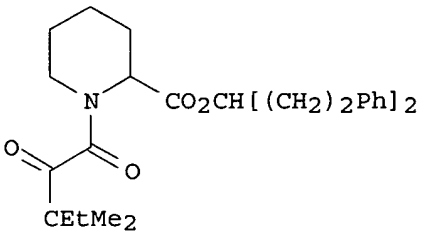
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009109	A2	20000224	WO 1999-US18242	19990812 <--
WO 2000009109	A3	20000817		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6376517	B1	20020423	US 1998-134417	19980814 <--
CA 2344520	AA	20000224	CA 1999-2344520	19990812 <--
AU 9955557	A1	20000306	AU 1999-55557	19990812 <--
EP 1109554	A2	20010627	EP 1999-942109	19990812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002522485	T2	20020723	JP 2000-564612	19990812 <--

PRIORITY APPLN. INFO.:

US 1998-134417	A	19980814
WO 1999-US18242	W	19990812

GI

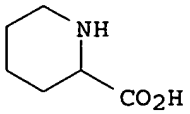


I

AB **Pipecolic** acid derivs. are prepared for treating vision disorders, improving vision, treating **memory** impairment, or enhancing **memory** performance in an animal. These compds. bind to immunophilin FKBP12 and preferably do not have immunosuppressive activity. Affinity for FKBP12 is measured as inhibition of prolyl peptidyl cis-trans isomerase (rotamase). Thus, **pipecolic** acid ester I inhibited rotamase with a Ki of 20 nM, showed a clearance rate of 41.8 μL/min, and rescued 56.6% of optic nerve axons from degeneration 14 days after optic nerve transection in rats (dose and route of administration not stated).

IT **535-75-1D**, **Pipecolic** acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pipecolic** acid derivs. for vision and **memory** disorders)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



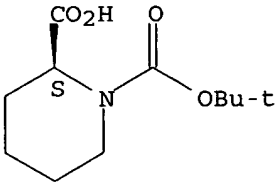
L36 ANSWER 27 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133480 HCAPLUS
DOCUMENT NUMBER: 132:175850
TITLE: Compositions and uses for vision and memory disorders
INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 175 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009108	A2	20000224	WO 1999-US18241	19990812 <--
WO 2000009108	A3	20000518		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335815	AA	20000224	CA 1999-2335815	19990812 <--
AU 9955556	A1	20000306	AU 1999-55556	19990812 <--
EP 1105112	A2	20010613	EP 1999-942108	19990812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002522484	T2	20020723	JP 2000-564611	19990812 <--
PRIORITY APPLN. INFO.:			US 1998-134422 A	19980814
			WO 1999-US18241 W	19990812

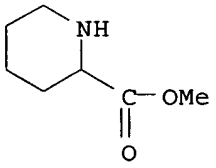
AB Nonimmunosuppressive FKBP neuroimmunophilin ligands, especially FKBP-12 ligands,
are useful for treating a vision disorder, improving vision, treating memory impairment, or enhancing memory performance in animals. Thus, GPI 1046 protected rat retinal ganglion cells and optic nerve axons and myelin against degeneration after retinal ischemia, and protected retinal ganglion cells against cell death after optic nerve transection. Another compound, (2S)-2-[(1-oxo-5-phenyl)pentyl]-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine, was prepared by Grignard reaction of 1-chloro-4-phenylbutane with N-benzyl-L-proline Et ester, debenzylation, and condensation with Me oxalyl chloride followed by 1,1-dimethylpropylmagnesium chloride.
IT **26250-84-0 41994-45-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(compns. and uses for vision and **memory** disorders)
RN 26250-84-0 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 41994-45-0 HCAPLUS
CN 2-Piperidinecarboxylic acid, methyl ester (9CI) (CA INDEX NAME)

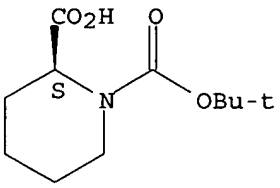


L36 ANSWER 28 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133479 HCAPLUS
DOCUMENT NUMBER: 132:175849
TITLE: N-linked sulfonamides of heterocyclic thioesters for vision and memory disorders
INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009107	A2	20000224	WO 1999-US18240	19990812 <--
WO 2000009107	A3	20000615		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2336148	AA	20000224	CA 1999-2336148	19990812 <--
AU 9955555	A1	20000306	AU 1999-55555	19990812 <--
EP 1105126	A2	20010613	EP 1999-942107	19990812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

JP 2002522483 T2 20020723 JP 2000-564610 19990812 <--
PRIORITY APPLN. INFO.: US 1998-134421 A 19980814
WO 1999-US18240 W 19990812
OTHER SOURCE(S): MARPAT 132:175849
AB The title compds. R1SO2N(A)CHBC(:X)SYZ(C)D [I; A and B complete a 5-7-membered heterocyclic ring; X = O, S; R1 = C1-6 (substituted) alkyl, C2-6 (substituted) alkenyl, (substituted) C3-8 cycloalkyl, aryl, heteroaryl; Y = bond, C1-6 (substituted) alkylene, C2-6 (substituted) alkenylene; Z = C1-6 (substituted) (hetero)alkylene, C2-6 (substituted) (hetero)alkenylene; C, D = H, aryl, C1-6 (substituted) (hetero)alkyl, C2-6 (substituted) (hetero)alkenyl] are prepared for treating vision disorders, improving vision, treating memory impairment, or enhancing memory performance in an animal. I bind to immunophilin FKBP12 and preferably do not have immunosuppressive activity. Affinity for FKBP12 is measured as inhibition of prolyl peptidyl cis-trans isomerase (rotamase). Thus, GPI 1046 (10 mg/kg s.c.) protected retinal ganglion cells and optic nerve axons and myelin against degeneration following retinal ischemia in rats, and protected against retinal ganglion cell death after optic nerve transection. 3-(P-Methoxyphenyl)-1-propylmercaptan (preparation given) was condensed with N-(tert-butyloxycarbonyl)-(S)-proline, and the product was deblocked and condensed with benzenesulfonyl chloride to form 3-(p-methoxyphenyl)-1-propylmercaptyl (2S)-N-(benzenesulfonyl)pyrrolidine-2-carboxylate [I, AB = Z = (CH2)3, X = O, R1 = Ph, Y = bond, C = C6H4OMe-p, D = H].
IT **26250-84-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-linked sulfonamides of heterocyclic thioesters for vision and **memory** disorders)
RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L36 ANSWER 29 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:133475 HCAPLUS
DOCUMENT NUMBER: 132:175846
TITLE: Small molecule sulfonamides for vision and memory disorders
INVENTOR(S): Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000009104	A2	20000224	WO 1999-US18232	19990812 <--
WO 2000009104	A3	20001207		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6333340	B1	20011225	US 1998-134473	19980814 <--
CA 2335810	AA	20000224	CA 1999-2335810	19990812 <--
AU 9954776	A1	20000306	AU 1999-54776	19990812 <--
EP 1105125	A2	20010613	EP 1999-941052	19990812 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002522480	T2	20020723	JP 2000-564607	19990812 <--

PRIORITY APPLN. INFO.:

US 1998-134473	A	19980814
WO 1999-US18232	W	19990812

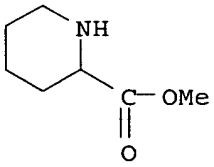
OTHER SOURCE(S): MARPAT 132:175846

AB Small-mol. sulfonamides JV(SO2E)CHKC(O)A(CH2)nCBD [I; A = CH2, O, NH, NG; G = C1-4 alkyl; B, D = H, (substituted) C1-6 alkyl, (substituted) C2-6 alkenyl, aryl; E = C1-6 alkyl, C2-6 alkenyl, C5-7 cycloalkyl, (substituted) C5-7 cycloalkenyl; J = H, Me, Et, PhCH2; K = C1-4 alkyl, PhCH2, cyclohexylmethyl; or J and K together complete a 5-7-membered heterocyclic ring; V = CH, N, S; n = 0-3] are prepared for treating vision disorders, improving vision, treating memory impairment, or enhancing memory performance in an animal. I bind to immunophilin FKBP12 and preferably do not have immunosuppressive activity. Affinity for FKBP12 is measured as inhibition of prolyl peptidyl cis-trans isomerase (rotamase). Thus, GPI 1046 (10 mg/kg s.c.) protected retinal ganglion cells and optic nerve axons and myelin following retinal ischemia in rats, and protected against retinal ganglion cell death after optic nerve transection. N-(tert-butyloxycarbonyl)-(S)-proline reacted with 3-(3-pyridyl)-1-propanol and deprotected to form 3-(3-pyridyl)-1-propylpyrrolidine-2-carboxylic acid, which was further condensed with α-toluenesulfonyl chloride to form 3-(3-pyridyl)-1-Pr (2S)-N-(α-toluenesulfonyl)pyrrolidine-2-carboxylic acid [I, A = O, CBD = 3-pyridyl, E = PhCH2, JK = (CH2)3; V = N].

IT **32559-18-5**, Methyl **pipecolinate** hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(small mol. sulfonamides for vision and **memory** disorders)

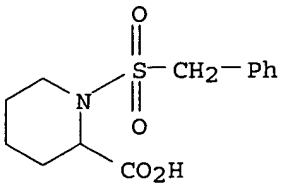
RN 32559-18-5 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



HCl

IT **204332-47-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(small mol. sulfonamides for vision and **memory** disorders)
RN 204332-47-8 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-[(phenylmethyl)sulfonyl]- (9CI) (CA INDEX NAME)



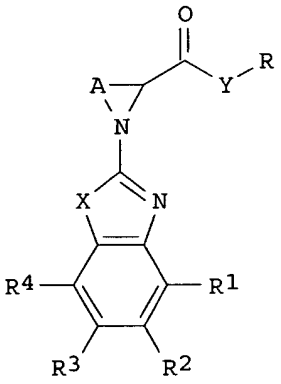
L36 ANSWER 30 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:84802 HCAPLUS
DOCUMENT NUMBER: 132:137377
TITLE: Preparation of benzoxazolyl piperidines and analogs as rotamase enzyme inhibitors
INVENTOR(S): Kemp, Mark Ian; Palmer, Michael John; Sanner, Mark Allen; Wythes, Martin James
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000005232	A1	20000203	WO 1999-IB1211	19990628 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2338214	AA	20000203	CA 1999-2338214	19990628 <--
AU 9942858	A1	20000214	AU 1999-42858	19990628 <--
AU 765925	B2	20031002		
BR 9912330	A	20010417	BR 1999-12330	19990628 <--
EP 1100797	A1	20010523	EP 1999-963123	19990628 <--
EP 1100797	B1	20030226		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
TR 200100135	T2	20010621	TR 2001-200100135	19990628 <--
EE 200100044	A	20020617	EE 2001-44	19990628 <--
JP 2002521382	T2	20020716	JP 2000-561188	19990628 <--
NZ 508838	A	20021220	NZ 1999-508838	19990628 <--
AT 233261	E	20030315	AT 1999-963123	19990628 <--
ES 2191484	T3	20030901	ES 1999-963123	19990628 <--

NZ 522270	A	20040326	NZ 1999-522270	19990628	<--
CN 1511837	A	20040714	CN 2003-10123907	19990628	<--
CN 1611499	A	20050504	CN 2004-10039974	19990628	
TW 229672	B1	20050321	TW 1999-88111868	19990713	
NO 2001000322	A	20010315	NO 2001-322	20010119	<--
HR 2001000052	A1	20011231	HR 2001-52	20010119	<--
BG 105254	A	20011031	BG 2001-105254	20010214	<--
JP 2004002374	A2	20040108	JP 2003-105099	20030409	<--
PRIORITY APPLN. INFO.:			GB 1998-15880	A 19980721	
			JP 2000-561188	A3 19990628	
			NZ 1999-508838	A1 19990628	
			WO 1999-IB1211	W 19990628	

OTHER SOURCE(S): MARPAT 132:137377

GI



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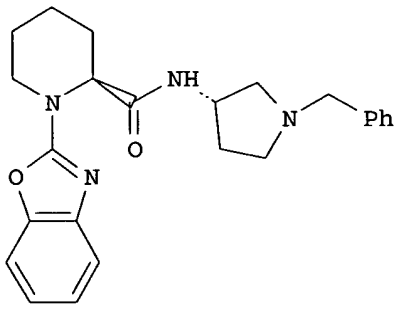


II

AB Title compds. (I) [wherein A = (un)substituted unbranched C3-C5 alkylene; X and Y = independently O, S, NH, or N-alkyl; R = (un)substituted, C-linked, 4- to 6-membered, non-aromatic, heterocyclic ring containing 1 N; R1-R4 = independently H, halo, (cyclo)alkyl, haloalkyl, (cyclo)alkoxy, CONR5R6, cycloalkylalkylene, cycloalkylalkoxy, or CO2R7; R5 and R6 = independently H, alkyl, or taken together = unbranched alkylene; R7 = alkyl] were prepared as rotamase enzyme inhibitors, particularly FKBP-12 and FKBP-52 inhibitors. Thus, (2S)-1-(1,3-benzoxazol-2-yl)-2-piperidinecarboxylic acid (preparation given) was amidated with (3S)-1-benzylpyrrolidine-3-ylamine in the presence of 1-hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.HCl in CH2Cl2 to yield II. Twenty-one compds. of the invention demonstrated inhibitory activity against human recombinant FKBP-12 in a coupled colorimetric PPIase in vitro assay with IC50 values below 1200 nM, and II inhibited the rotamase enzyme FKBP-52 in a similar assay with IC50 = 2790 nM. As neurotrophic agents, the invention compds. promote neuronal regeneration and outgrowth and are useful for the treatment of neurodegenerative diseases or other disorders involving nerve damage.

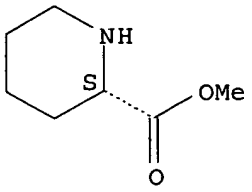
IT **18650-39-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of benzoxazolyl piperidine derivs. and analogs as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)

RN 18650-39-0 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride, (2S)- (9CI) (CA

INDEX NAME)

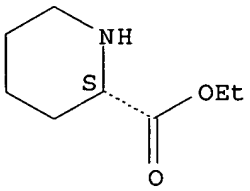
Absolute stereochemistry. Rotation (-).



● HCl

IT **22328-78-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of benzoxazolyl piperidine derivs. and analogs as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)
RN 22328-78-5 HCAPLUS
CN 2-Piperidinecarboxylic acid, ethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 31 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:84800 HCAPLUS
DOCUMENT NUMBER: 132:137376
TITLE: Preparation of benzoxazolyl and benzimidazolyl piperidines as FKBP inhibitors
INVENTOR(S): Wythes, Martin James; Palmer, Michael John; Kemp, Mark Ian; Mackenny, Malcolm Christian; Maguire, Robert John; Blake, James Francis, Jr.
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.; Blake, James Francis, Jr.
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000005231	A1	20000203	WO 1999-IB1227	19990701 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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AU 9943855	A1	20000214	AU 1999-43855		19990701 <--
AU 756769	B2	20030123			
BR 9912307	A	20010502	BR 1999-12307		19990701 <--
EP 1098894	A1	20010516	EP 1999-926683		19990701 <--
EP 1098894	B1	20021002			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
TR 200100133	T2	20010621	TR 2001-200100133		19990701 <--
EE 200100043	A	20020617	EE 2001-43		19990701 <--
JP 2002521381	T2	20020716	JP 2000-561187		19990701 <--
JP 3545341	B2	20040721			
AT 225346	E	20021015	AT 1999-926683		19990701 <--
NZ 508839	A	20030131	NZ 1999-508839		19990701 <--
PT 1098894	T	20030228	PT 1999-926683		19990701 <--
ES 2183567	T3	20030316	ES 1999-926683		19990701 <--
US 6166011	A	20001226	US 1999-354193		19990715 <--
US 6495549	B1	20021217	US 2000-699878		20001030 <--
US 6509464	B1	20030121	US 2000-699869		20001030 <--
US 6686357	B1	20040203	US 2000-699752		20001030 <--
ZA 2001000229	A	20020409	ZA 2001-229		20010109 <--
NO 2001000299	A	20010315	NO 2001-299		20010118 <--
HR 2001000053	A1	20011231	HR 2001-53		20010119 <--
BG 105249	A	20011130	BG 2001-105249		20010214 <--
US 2004058905	A1	20040325	US 2003-404524		20030401 <--
PRIORITY APPLN. INFO.:			GB 1998-15696	A	19980720
			WO 1999-IB1227	W	19990701
			US 1999-354193	A3	19990715
			US 2000-699752	A1	20001030

OTHER SOURCE(S): MARPAT 132:137376
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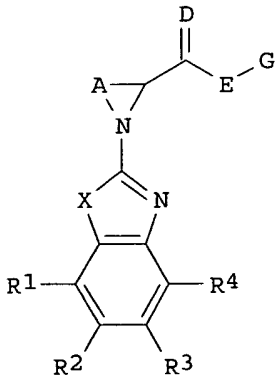

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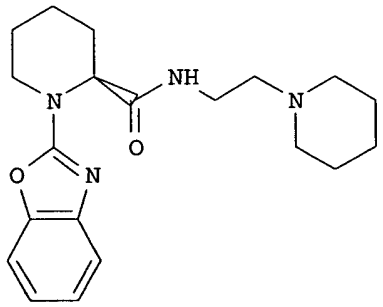


II

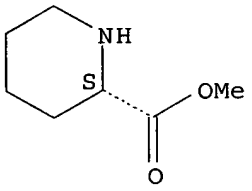
AB Title compds. (I) [wherein X = O, S, NH, or N-alkyl; R1-R4 = independently H, OH, OCOR5, CO2R5, CONH2, CONHR5, CONR52, halo, cycloalkyl(oxy), alkenyl, aryl, and (un)substituted alkyl(oxy); R5 = alkyl; A =

(un)substituted unbranched alkylene; D = O or S; E = O, S, NH, N-alkyl, or (un)substituted methylene; G = (un)substituted alkyl or alkenyl] were prepared as rotamase enzyme inhibitors, particularly FKBP-12 and FKBP-52 inhibitors. Thus, (2S)-1-(1,3-benzoxazol-2-yl)-2-piperidinecarboxylic acid (preparation given) was amidated with 2-piperidinoethylamine in the presence of N-methylmorpholine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.HCl in CH2Cl2 to yield (S)-II. Eight compds. of the invention demonstrated FKBP-inhibiting activity vs. human recombinant FKBP-12 and/or FKBP-52 in coupled colorimetric PPIase in vitro assays with IC50 and Ki,app values below 1μM. As neurotrophic agents, the invention compds. promote neuronal regeneration and outgrowth and are useful for the treatment of neuronal degeneration and neurol. disorders.

IT **18650-39-0P 26250-84-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of benzoxazolyl and benzimidazolyl piperidine derivs. as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)

RN 18650-39-0 HCAPLUS
CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride, (2S)- (9CI) (CA INDEX NAME)

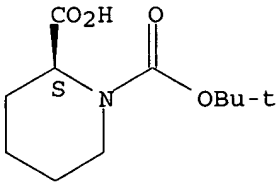
Absolute stereochemistry. Rotation (-).



● HCl

RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

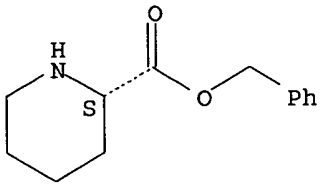
Absolute stereochemistry. Rotation (-).



IT **149201-79-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of benzoxazolyl and benzimidazolyl piperidine derivs. as FKBP inhibitors for the treatment of neuronal degeneration and neurol. disorders)

RN 149201-79-6 HCAPLUS
CN 2-Piperidinecarboxylic acid, phenylmethyl ester, hydrochloride, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 32 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:84623 HCAPLUS
DOCUMENT NUMBER: 132:122528
TITLE: Preparation of benzoquinolizidines and benzoindolizidines for treatment of neurodegenerative states and diseases associated with memory impairment
INVENTOR(S): Szmuszkovicz, Jacob; Regan, Ciaran M.
PATENT ASSIGNEE(S): American Biogenetic Sciences, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2000004905	A1	20000203	WO 1999-US16432		19990720	<--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG						
CA 2338222	AA	20000203	CA 1999-2338222		19990720	<--
AU 9950050	A1	20000214	AU 1999-50050		19990720	<--
EP 1098650	A1	20010516	EP 1999-934157		19990720	<--
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US 6436954	B1	20020820	US 2001-744183		20010314	<--
PRIORITY APPLN. INFO.:			US 1998-93617P	P	19980721	
			WO 1999-US16432	W	19990720	

OTHER SOURCE(S): MARPAT 132:122528
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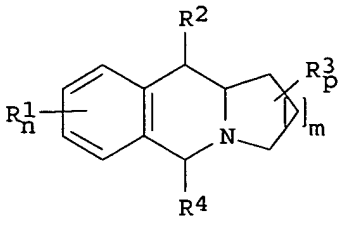


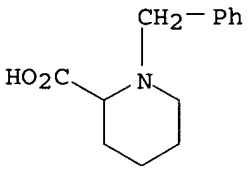
I

AB The title compds. [I; n = 1-4; R1 = H, halo, alkyl, etc.; R2 = OR5, NR6R7; R5 = alkyl, cycloalkyl, alkanoyl, etc.; R6, R7 = H, alkyl, cycloalkyl, etc.; NR6R7 = azetidino, pyrrolidino, piperidino, morpholino; p = 1-6; R3 = H, OH, alkoxy, etc.; R4 = H, alkyl, cycloalkyl, aryl, etc.; m = 1-4], useful for the treatment of Alzheimer's disease, senile dementia, or other conditions characterized by memory loss, were prepared E.g., a multi-step synthesis of trans-I [R1 = R3 = R4 = H; m = 2; R2 = NHMe] was presented. Biol. data (e.g., acetylcholinesterase activity) for compds. I were given.

IT **21319-53-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzoquinolizidines and benzoindolizidines for treatment of **neurodegenerative** states and diseases associated with **memory** impairment)

RN 21319-53-9 HCAPLUS

CN 2-Piperidinecarboxylic acid, 1-(phenylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 33 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:748312 HCAPLUS

DOCUMENT NUMBER: 131:351237

TITLE: Preparation of heterocyclic thioesters and ketones, and particularly substituted pyrrolidine- and piperidinecarbothioate derivatives, as neurotrophic agents

INVENTOR(S): Hamilton, Gregory S.; Li, Jia-he

PATENT ASSIGNEE(S): Gpi Nil Holdings Inc., USA

SOURCE: U.S., 23 pp., Cont.-in-part of U.S. Ser. No. 721,765. CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5990131	A	19991123	US 1997-904461	19970801 <--
US 5786378	A	19980728	US 1996-721765	19960925 <--

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    ZA 9707900          A     19990503    ZA 1997-7900          19970903 <--
    CA 2263927          AA    19980402    CA 1997-2263927       19970909 <--
    WO 9813343          A1    19980402    WO 1997-US15832       19970909 <--
        W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
            DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ,
            LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU
        RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
            GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
            GN, ML, MR, NE, SN, TD, TG
    AU 9742590          A1    19980417    AU 1997-42590         19970909 <--
    AU 739361           B2    20011011
    EP 934263           A1    19990811    EP 1997-940917        19970909 <--
    EP 934263           B1    20051123
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO
    BR 9713202          A     20000404    BR 1997-13202         19970909 <--
    NZ 334315           A     20001124    NZ 1997-334315        19970909 <--
    CN 1275977          A     20001206    CN 1997-198199        19970909 <--
    JP 2001506231       T2    20010515    JP 1998-515667        19970909 <--
    NZ 507720           A     20030429    NZ 1997-507720        19970909 <--
    SG 109418           A1    20050330    SG 2000-200001995     19970909
    AT 310722           E     20051215    AT 1997-940917        19970909
    EP 1626043          A1    20060215    EP 2005-25042         19970909
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, AL
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    KR 2000048591       A     20000725    KR 1999-702525        19990324 <--
    US 6218424          B1    20010417    US 1999-444200        19991122 <--
    US 2001056103       A1    20011227    US 2000-733037        20001211 <--
    US 6417209          B2    20020709
    AU 2001057861       A5    20020801    AU 2001-57861         20010808 <--
    AU 777188           B2    20041007
    US 2002193420       A1    20021219    US 2002-104242        20020325 <--
    NZ 518473           A     20050128    NZ 2002-518473        20020419
    US 2004106652       A1    20040603    US 2003-615803        20030710 <--
    US 6984639          B2    20060110
    US 2005148637       A1    20050707    US 2005-70505         20050303
PRIORITY APPLN. INFO.:                      US 1996-721765     A2 19960925
                                            US 1997-904461     A  19970801
                                            EP 1997-940917     A3 19970909
                                            WO 1997-US15832    W  19970909
                                            US 1999-444200     A3 19991122
                                            US 2000-733037     A1 20001211
                                            US 2002-104242     B1 20020325
                                            US 2003-615803     A3 20030710
OTHER SOURCE(S):        MARPAT 131:351237
GI
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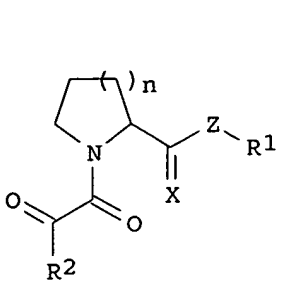

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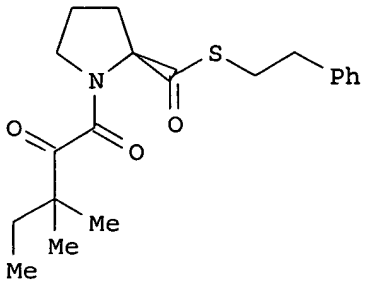


II

AB The invention relates to neurotrophic, low mol. weight, small mol. heterocyclic thioesters and ketones, specifically I [n = 1 or 2; X = O or S; Z = S, CH2, CHR1 and C(R1)2 ; R1 = C1-C5 straight or branched chain alkyl, C2-C5 straight or branched chain alkenyl, Ar1 and mixts. thereof, wherein R1 may be substituted with halo, NO2, C1-C6 straight or branched chain alkyl, C2-C6 straight or branched chain alkenyl, OH, C1-C4 alkoxy, C2-C4 alkenyloxy, PhO, PhCH2O, amino, Ar1, or a mixture thereof; R2 = C1-C9 straight or branched chain alkyl, C2-C9 straight or branched chain alkenyl, C3-C8 cycloalkyl, C5-C7 cycloalkenyl, and Ar1; Ar1 = Ph, PhCH2, pyridyl, fluorenyl, thioindolyl [sic; benzothienyl] or naphthyl, wherein Ar1 may be substituted with halo, OH, NO2, C1-C6 straight or branched chain alkyl, C2-C6 straight or branched chain alkenyl, C1-C4 alkoxy, C2-C4 alkenyloxy, PhO, PhCH2O, or amino] or their pharmaceutically acceptable salts. The compds. have an affinity for FKBP-type immunophilins, and are potent inhibitors of the enzyme activity associated with immunophilin proteins, particularly peptidyl-prolyl cis-trans isomerase (rotamase) enzyme activity. The compds. may be used to prevent or repair nerve damage, or to prevent the side effects of immunosuppressants. For instance, L-proline Me ester HCl underwent a sequence of: (1) N-acylation with ClCOCOOMe; (2) Grignard reaction with EtMe2CMgCl; (3) ester saponification; and (4) thioesterification with PhCH2CH2SH, to give title compound II. When coadministered at 4 mg/kg s.c. to mice in the MPTP (neurotoxin) model of Parkinson's disease, II gave 61% recovery from lesioning of striatal dopaminergic neurons as determined by tyrosine hydroxylase function.

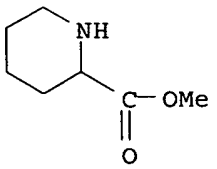
IT **130939-66-1**, **Neurotrophin**-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing; preparation of substituted pyrrolidine- and piperidinecarbothioate derivs. as neurotrophic agents)

RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **32559-18-5**, Methyl **pipecolate** hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of substituted pyrrolidine- and piperidinecarbothioate derivs. as neurotrophic agents)

RN 32559-18-5 HCAPLUS
CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

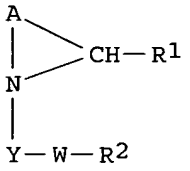
L36 ANSWER 34 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:617440 HCAPLUS
TITLE: Synthesis of ketone analogs of prolyl and **pipecolyl** ester FKBP12 ligands.
AUTHOR(S): Wu, Yong; Wilkinson, Doug; Limburg, David; Li, Jia-He; Sauer, Hansjorg; Ross, Doug; Liang, Shi; Spicer, Dawn; Valentine, Heather; Fuller, Mike; Guo, Hong; Howorth, Pam; Soni, Rajit; Chen, Yi; Steiner, Joe; Hamilton, Greg
CORPORATE SOURCE: Dept. of Research, Guilford Pharmaceuticals, Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (**1999**), MEDI-069. American Chemical Society: Washington, D. C. CODEN: 67ZJA5
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The recent discovery that nonimmunosuppressant ligands for the immunophilin FKBP12 promote regeneration of damaged nerves in vitro and in vivo has prompted considerable interest in exploring such structures. We have previously reported in detail on the therapeutic utility of one such FKBP12 ligand, GPI 1046, in a variety of animal models of **neurodegenerative** disease. The FKBP ligands reported to date have been esters of proline or **pipecolic** acid. As part of our program to explore several structural classes of FKBP12 ligands, we were interested in preparing ketone analogs of our previously described compds. Synthesis of keto analogs of proline is frequently difficult, and no general methods exist in the literature. We have developed an efficient method for the synthesis of these compds. utilizing Grignard chemical for formation of an unsatd. ketone intermediate followed by palladium-mediated Heck coupling to introduce a variety of substituents. Details of the synthetic studies, together with a comparison of the biol. activity of some of the ketones with their ester analogs, will be described.

L36 ANSWER 35 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:576925 HCAPLUS
DOCUMENT NUMBER: 131:214289
TITLE: Preparation of oxadiazolyl piperidine derivatives as rotamase enzyme inhibitors
INVENTOR(S): Bull, David John; MaGuire, Robert John; Palmer, Michael John; Wythes, Martin James
PATENT ASSIGNEE(S): Pfizer Inc., USA; Pfizer Ltd.
SOURCE: PCT Int. Appl., 237 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9945006	A1	19990910	WO 1999-IB259	19990215 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2322442	AA	19990910	CA 1999-2322442	19990215 <--
AU 9921810	A1	19990920	AU 1999-21810	19990215 <--
BR 9908480	A	20001205	BR 1999-8480	19990215 <--
EP 1060178	A1	20001220	EP 1999-901847	19990215 <--
EP 1060178	B1	20030903		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002505329	T2	20020219	JP 2000-534548	19990215 <--
JP 3668133	B2	20050706		
AT 248836	E	20030915	AT 1999-901847	19990215 <--
PT 1060178	T	20031231	PT 1999-901847	19990215 <--
ES 2204101	T3	20040416	ES 1999-901847	19990215 <--
US 6610707	B1	20030826	US 1999-380427	19990901 <--
PRIORITY APPLN. INFO.:			GB 1998-4426 A	19980302
			WO 1999-IB259 W	19990215

OTHER SOURCE(S): MARPAT 131:214289
GI



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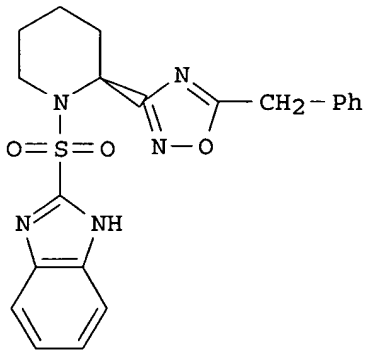


II

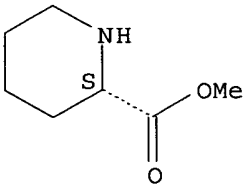
AB Oxadiazolyl piperidine derivs. and analogs (I) [R1 = 5- or 6-membered heteroaryl (un)substituted ring containing 1-4 N, or 1 S or O and/or 1-2 N atoms; R2 = H, (un)substituted Ph, (un)substituted C3-7 cycloalkyl, or 5-, 6-, or 7-membered (un)substituted heterocycle; A = C3-5 alkylene; W = direct link, C1-6 alkylene, or C2-6 alkenylene; X = direct link, C1-6 alkylene, or alkylene-Z-alkylene; Y = SO2, CO, (un)substituted CO-NH, CO-CO, CH2-CO, CS-CO, CO-CS, or CO-CH(OH); Z = O, S, (un)substituted CH2-NH, CH(aryl), NH, NH-CO2, CO-NH, or NH-CO] were prepared as rotamase

enzyme inhibitors, particularly FKBP-12 and FKBP-52 inhibitors, to moderate neuronal regeneration and outgrowth. Thus, ethyldiisopropylamine was added to a mixture of 5-benzyl-3-[(2S)-2-piperidyl]-1,2,4-oxadiazole hydrochloride (preparation given) and 1H-benzo[d]imidazole-2-sulfonyl chloride (preparation given) in CH2Cl2 and the mixture was stirred for 18 h to yield 1H-benzo[d]imidazol-2-yl [(2S)-2-(5-benzyl-1,2,4-oxadiazol-3-yl)-1-piperidyl] sulfone (II). Seven compds. of the invention were tested for in vitro inhibitory activity against the FKBP-12 enzyme in a coupled colorimetric PPIase assay, and exhibited IC50 values in the range of 81 nm to 2010 nm. One compound was assayed for inhibitory activity against the FKBP-52 enzyme and gave a Ki value of 685. The compds. are claimed to be useful in treating neurol. disorders arising from neurodegenerative diseases and nerve damage.

IT **18650-39-0P 26250-84-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of oxadiazolyl piperidine derivs. as rotamase enzyme inhibitors for treatment of neurol. disorders arising from **neurodegenerative diseases** and **nerve** damage)

RN 18650-39-0 HCAPLUS
CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride, (2S)- (9CI) (CA INDEX NAME)

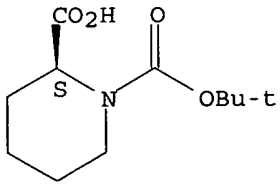
Absolute stereochemistry. Rotation (-).



● HCl

RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 36 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:166610 HCAPLUS
DOCUMENT NUMBER: 130:209979

TITLE: Preparation of N-sulfonylamino acid amides and related compounds for promotion of neuronal repair.
INVENTOR(S): McCaffrey, Patricia; Novak, Perry M.; Mullican, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9910340	A1	19990304	WO 1998-US17816		19980827 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6268384	B1	20010731	US 1998-85441		19980527 <--
CA 2300134	AA	19990304	CA 1998-2300134		19980827 <--
AU 9889236	A1	19990316	AU 1998-89236		19980827 <--
AU 766579	B2	20031016			
EP 1007521	A1	20000614	EP 1998-941093		19980827 <--
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BR 9811923	A	20000815	BR 1998-11923		19980827 <--
JP 2001514177	T2	20010911	JP 2000-507669		19980827 <--
NZ 502820	A	20021025	NZ 1998-502820		19980827 <--
NO 2000000953	A	20000502	NO 2000-953		20000225 <--
MX 200002100	A	20001230	MX 2000-2100		20000229 <--
PRIORITY APPLN. INFO.:			US 1997-920838	A	19970829
			US 1998-85441	A	19980527
			WO 1998-US17816	W	19980827

OTHER SOURCE(S): MARPAT 130:209979

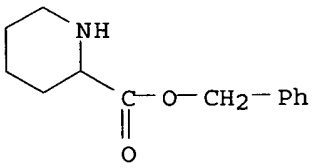
AB DSO2N(J)(CH2)nCHKCOX(Y)CHBA [A, B = H, Ar, (O-, S-, SO-, SO2-, or NR-interrupted) alkyl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, etc.; R = H, alkyl, alkenyl, alkynyl; Ar = (substituted) Ph, naphthyl, indenyl, azulenyl, fluorenyl, furyl, pyridyl, pyrrolyl, oxazolyl, pyrazolidnyl, isothiazolyl, etc.; X = N, O, CR; Y = H, Ar, alkyl, alkenyl, alkynyl, cycloalkylalkyl, aralkyl, electron pair, etc.; J = H, alkyl, alkenyl, alkynyl, aralkyl, aralkenyl, aralkynyl, cyclohexylmethyl; D = Ar, (O-, S-, SO-, SO2-, or NR-interrupted) alkyl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, aralkyl, etc.; n = 0-2], and related compds., were prepared Thus, (S)-piperidine-1,2-dicarboxylic acid 1-tert-Bu ester in CH2Cl2 was treated with EDC and 2-(2-methylaminoethyl)pyridine followed by 24 h stirring to give 50% (S)-piperidine-1,2-dicarboxylic acid 1-tert-Bu ester 2-[(N-methyl)-2-pyridinylethyl]amide. The latter was treated with CF3CO2H in CH2Cl2 to give 81% (S)-piperidine-2-carboxylic acid 2-[(N-methyl)-2-pyridinylethyl]amide. This was stirred with 4-O2NC6H4SO2Cl and Et3N in CH2Cl2 to give 78% nitrobenzenesulfonamide derivative, which was hydrogenated in EtOAc over Pd/C to give 40% N-(4-aminobenzenesulfonamido)-(S)-piperidine-2-carboxylic acid 2-[(N-methyl)-2-pyridylethyl]amide. Title compds. at 1000 nM in pheochromocytoma P12 cells gave neurite outgrowth of 2-4 on a scale of

0-4.

IT **130939-66-1, Neurotrophin-3 143375-33-1, Neurotrophin-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. with neurotrophic compds.; preparation of N-sulfonylamino acid amides and related compds. for promotion of neuronal repair)
RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 143375-33-1 HCAPLUS
CN Neurotrophin 4/5 (9CI) (CA INDEX NAME)

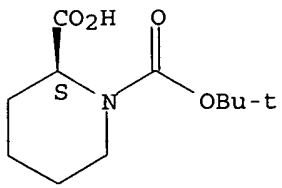
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **38068-75-6 143375-33-1, Neurotrophin-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of N-sulfonylamino acid amides and related compds. for promotion of neuronal repair)
RN 38068-75-6 HCAPLUS
CN 2-Piperidinecarboxylic acid, phenylmethyl ester (9CI) (CA INDEX NAME)



RN 143375-33-1 HCAPLUS
CN Neurotrophin 4/5 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **26250-84-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of N-sulfonylamino acid amides and related compds. for promotion of neuronal repair)
RN 26250-84-0 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 37 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:92752 HCAPLUS
TITLE: Structural analysis of the binding of neurotrophic ligands for FKBP12
AUTHOR(S): Thomas, Christine; Wei, Ling; Holmes, Agnes; Soni, Rajit; Connolly, Maureen; Steiner, Joseph P.; Summers, Michael F.; Hamilton, Gregory S.
CORPORATE SOURCE: Guilford Pharmaceuticals, Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (**1999**), MEDI-238. American Chemical Society: Washington, D. C.
CODEN: 67GHA6
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The immunophilin FKBP12 is a member of the large family of proteins which possess peptidylprolyl isomerase or PPIase activity. It has recently been demonstrated that nonimmunosuppressant small mol. ligands for FKBP12 possess the remarkable ability to promote regeneration of damaged peripheral and central nerves following oral administration. GPI 1046 is a prolyl competitive inhibitor of FKBP12 which has demonstrated therapeutic utility in a variety of animal models of **neurodegeneration.** We have determined the solution structure of the GPI 1046/FKBP12 complex by multidimensional NMR, and compared the binding of GPI 1046 to **pipecolic** acid analogs previously reported. We have also examined the binding of different structural classes of FKBP12 ligand by HSQC expts.

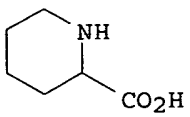
L36 ANSWER 38 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:92751 HCAPLUS
TITLE: Synthesis of thioester FKBP12 ligands and evaluation of their in vitro and in vivo nerve regenerative effects
AUTHOR(S): Limburg, David C.; Vaal, Mark J.; Li, Jia-He; Wu, Yong-Qian; Thomas, Christine; Sauer, Hansjorg; Ross, Douglas T.; Soni, Rajit; Chen, Yi; Guo, Hongshi; Howorth, Pamela; Valentine, Heather; Liang, Shi; Spicer, Dawn; Fuller, Mike; Steiner, Joseph P.; Hamilton, Gregory S.
CORPORATE SOURCE: Guilford Pharmaceuticals, Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (**1999**), MEDI-237. American Chemical Society: Washington, D. C.
CODEN: 67GHA6
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Ligands for the peptidyl-prolyl isomerase FKBP12 have been found to unexpectedly possess powerful neuroprotective and neuroregenerative effects in vitro and in vivo. We have extensively explored the therapeutic utility of FKBP12 ligands based on esters of proline and **pipecolic** acid. Here we describe a new class of FKBP12 ligand containing a thioester linkage. These novel FKBP12 ligands are effective in a rodent model of **Parkinson**'s Disease following either systemic or oral administration. Details of the in vitro SAR of these compds. as FKBP12 inhibitors, and their in vivo efficacy as neuroregenerative agents, will be discussed.

L36 ANSWER 39 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:763566 HCAPLUS
DOCUMENT NUMBER: 130:166668
TITLE: Defective peroxisome biogenesis with a neuromuscular disorder resembling Werdnig-Hoffmann disease
AUTHOR(S): Baumgartner, M. R.; Verhoeven, N. M.; Jakobs, C.; Roels, F.; Espeel, M.; Martinez, M.; Rabier, D.; Wanders, R. J. A.; Saudubray, J. M.
CORPORATE SOURCE: Department of Pediatrics, Hopital Necker-Enfants Malades, Paris, 75743, Fr.
SOURCE: Neurology (**1998**), 51(5), 1427-1432
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors characterized a defect in a patient presenting a peripheral **neuropathy** with atypical features of distal motor involvement mimicking Werdnig-Hoffmann disease. Clin. signs included generalized hypotonia and floppiness, absence of stretch reflexes, muscle wasting, lack of head control and lingual fasciculations associated with unaffected facial muscles, and normal intellectual development. Normal muscle histol. ruled out Werdnig-Hoffmann disease. Elevated plasma concns. of very long-chain fatty acids and bile acid intermediates combined with normal plasmalogen levels in erythrocytes suggested defective peroxisomal β-oxidation directly demonstrated by deficient pristanic acid and partially deficient C26:0 was present oxidation in cultured fibroblasts. Severely impaired **pipecolic** acid oxidation in liver and phytanic acid oxidation in fibroblasts was present. On light and electron microscopy of the liver tissue, rare peroxisomal membrane ghosts and trilamellar inclusions but absence of peroxisomes was noted. Immunoblot anal. revealed absence of peroxisomal β-oxidation enzymes in liver tissue but normal results in fibroblasts. Remarkably, expression of the peroxisomal defect in fibroblasts was indicated by the finding of mainly cytoplasmic catalase, as in liver. Preliminary studies excluded classification of this patient within the large PEX1 complementation group. The results suggest a novel peroxisome biogenesis disorder involving peroxisomal β-oxidation as well as phytanic and **pipecolic** acid oxidation rather than an isolated defect of peroxisomal β-oxidation The association of a clin. picture mimicking Werdnig-Hoffmann disease with a novel peroxisomal disorder raises the question of whether investigation for peroxisomal function should be considered in every patient with an enigmatic spinal muscular atrophy-like syndrome.

IT **535-75-1**, **Pipecolic** acid
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(of plasma in peroxisome biogenesis defect in human neuromuscular disorder resembling Werdnig-Hoffmann disease)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

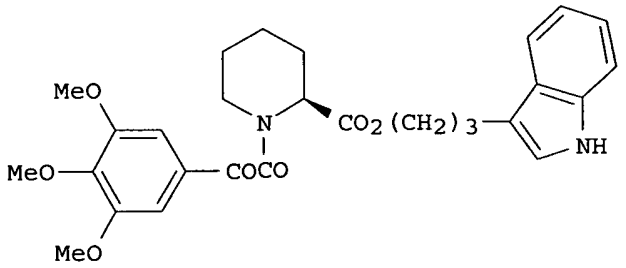
L36 ANSWER 40 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:603675 HCAPLUS
DOCUMENT NUMBER: 129:325735
TITLE: Investigations of Neurotrophic Inhibitors of FK506 Binding Protein via Monte Carlo Simulations
AUTHOR(S): Lamb, Michelle L.; Jorgensen, William L.
CORPORATE SOURCE: Department of Chemistry, Yale University, New Haven, CT, 06520-8107, USA
SOURCE: Journal of Medicinal Chemistry (**1998**), 41(21), 3928-3939
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding and solution-phase properties of six inhibitors of FK506 binding protein (FKBP12) were investigated using free energy perturbation techniques in Monte Carlo statistical mechanics simulations. These nonimmunosuppressive mols. are of current interest for their neurotrophic activity when bound to FKBP12 as well as for their potential as building blocks for chemical inducers of protein dimerization. Relative binding affinities were computed and analyzed for ligands differing by a Ph ring, an external Ph or pyridyl substituent, and a **pipecolyl** or prolyl ring. Such results are, in general, valuable for inhibitor optimization and, in the present case, bring into question some of the previously reported binding data.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 41 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:599365 HCAPLUS
DOCUMENT NUMBER: 129:198015
TITLE: Rotamase enzyme activity inhibitors
INVENTOR(S): Steiner, Joseph P.; Hamilton, Gregory S.
PATENT ASSIGNEE(S): GPI Nil Holdings, Inc., USA
SOURCE: U.S., 16 pp., Cont.-in-part of U. S. Ser. No. 551,026, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

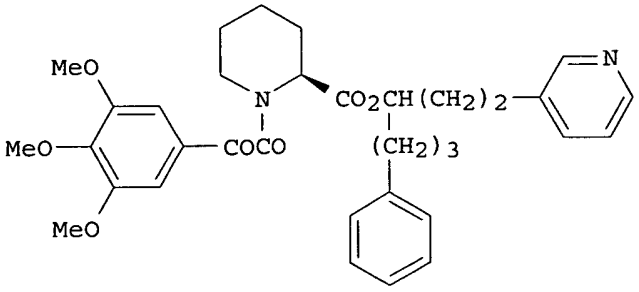
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5801197	A	19980901	US 1996-645149	19960513 <--
US 2002013344	A1	20020131	US 1995-551026	19951031 <--
CA 2236328	AA	19970509	CA 1996-2236328	19960826 <--
WO 9716190	A1	19970509	WO 1996-US13624	19960826 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9668573	A1	19970522	AU 1996-68573	19960826 <--
AU 713302	B2	19991125		
EP 859614	A1	19980826	EP 1996-929014	19960826 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI				

CN 1205635	A	19990120	CN 1996-199127		19960826 <--
JP 11514643	T2	19991214	JP 1996-517308		19960826 <--
NO 9801903	A	19980630	NO 1998-1903		19980427 <--
LV 12102	B	19981020	LV 1998-85		19980625 <--
PRIORITY APPLN. INFO.:			US 1995-551026	B2	19951031
			US 1996-645149	A	19960513
			WO 1996-US13624	W	19960826

OTHER SOURCE(S): MARPAT 129:198015
GI



I



II

AB This invention relates to the method of using specially formulated neurotrophic **pipecolic** acid derivative compds. having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or promote neuronal growth or regeneration. The stimulation of neurite outgrowth induced by a 300pM dose of I and 1 nM dose of II were demonstrated.

REFERENCE COUNT: 173 THERE ARE 173 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 42 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:529589 HCAPLUS
TITLE: N-glyoxyl prolyl and **pipecolyl** amide FKBP12 ligands: Potent neurotrophic agents in an animal model of **parkinson**'s disease
AUTHOR(S): Wu, Yong-Qian; Wilkinson, Doug; Soni, Raj; Scott, Chad; Ross, Douglas T.; Guo, Hong; Howorth, Pamela; Chen, Yi; Valentine, Heather; Liang, Shi; Spicer, Dawn; Steiner, Joseph; Hamilton, Gregory

CORPORATE SOURCE: Dept. Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (**1998**), MEDI-103. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB The recent discovery that small mol. ligands for the peptidyl-prolyl isomerae (PPIase) FKBP12 possess powerful neuroprotective and neuroregenerative properties in vitro and in vivo suggests therapeutic utility for such compds. in **neurodegenerative** disease. The neurotrophic effects of these compds. are independent of the immunosuppressive pathways by which drugs such as FK506 and rapamycin operate. Previous work by ourselves and other groups exploring the SAR of small mols. which mimic only the FKBP-binding domain portion of FK506 have focused on esters of proline and **pipecolic** acid. We have explored amide analogs of these earlier structures and found that they too are active in a mouse model of **Parkinson**'s Disease. Several compds. were shown to be effective upon oral administration subsequent to lesioning of the dopaminergic pathway, providing further evidence of the potential clin. utility of a variety of structural classes of FKBP12 ligands.

L36 ANSWER 43 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:338140 HCAPLUS
DOCUMENT NUMBER: 129:27895
TITLE: Preparation of 1-carbamoylpiperidine-2-carboxylates and analogs as neurotrophic factor adjuncts
INVENTOR(S): Zelle, Robert E.; Su, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9820893	A1	19980522	WO 1997-US20868	19971113 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5780484	A	19980714	US 1996-749114	19961113 <--
CA 2270985	AA	19980522	CA 1997-2270985	19971113 <--
ZA 9710248	A	19980528	ZA 1997-10248	19971113 <--
AU 9854397	A1	19980603	AU 1998-54397	19971113 <--
AU 741186	B2	20011122		
EP 941113	A1	19990915	EP 1997-948309	19971113 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1239434	A	19991222	CN 1997-180248	19971113 <--
IN 183409	A	19991225	IN 1997-CA2147	19971113 <--
BR 9713037	A	20000411	BR 1997-13037	19971113 <--

NZ 335396	A	20001124	NZ 1997-335396	19971113	<--
JP 2001503778	T2	20010321	JP 1998-522867	19971113	<--
TW 509572	B	20021111	TW 1997-86116912	19971113	<--
EP 1666053	A1	20060607	EP 2006-328	19971113	

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, AL

PRIORITY APPLN. INFO.:	US 1996-749114	A	19961113
	EP 1997-948309	A3	19971113
	WO 1997-US20868	W	19971113

OTHER SOURCE(S): MARPAT 129:27895

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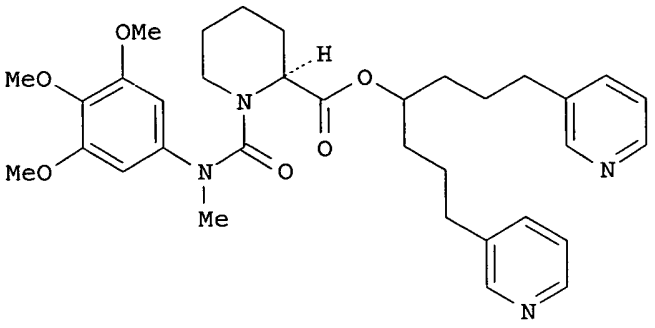


I

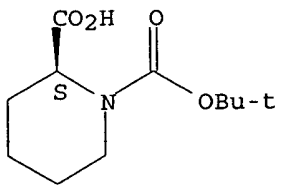
AB RC(:X)NR3CHR4COZ(CH2)mCHR5R6 [R = aryloxy, alkoxy, NR1R2; R1,R5,R6 = H, alkyl, aryl, etc.; R2 = alk(en)yl, alkynyl, aryl; R3 = H, alk(en)yl, arylmethyl; R4 = alkyl, arylmethyl, cyclohexylmethyl; R3R4 = atoms to complete a ring; X = O or S; Z = CH2, O, NR1; n = 0 or 1] were prepared as neurotrophic factor adjuncts for stimulation of neurite outgrowth (no data). Thus, (HC.tplbond.CCH2)2CHOH was bisarylated by 3-bromopyridine and the reduced product esterified by (S)-1-tert-butoxycarbonylpiperidine-2-carboxylic acid to give, after deprotection and condensation with 3,4,5-(MeO)3C6H2NHMe and COCl2, title compound I.

IT **26250-84-0**, (S)-Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 1-carbamoylpiperidine-2-carboxylates and analogs as neurotrophic factor adjuncts)

RN 26250-84-0 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

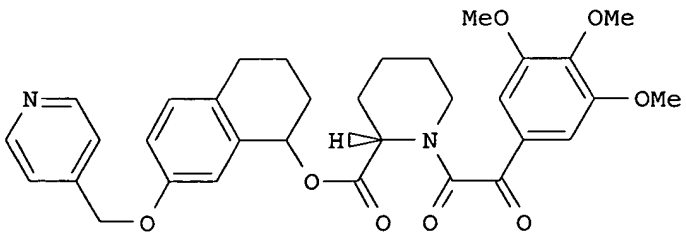


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 44 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:338139 HCAPLUS
DOCUMENT NUMBER: 129:27894
TITLE: Preparation of 1-tetralyl 1-oxoaracetylpiperidine-2-carboxylates and analogs as neurotrophic factor adjuncts
INVENTOR(S): Zelle, Robert E.; Su, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9820892	A1	19980522	WO 1997-US20867	19971113 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5811434	A	19980922	US 1996-748448	19961113 <--
CA 2270629	AA	19980522	CA 1997-2270629	19971113 <--
ZA 9710258	A	19980528	ZA 1997-10258	19971113 <--
AU 9854396	A1	19980603	AU 1998-54396	19971113 <--
EP 941112	A1	19990915	EP 1997-948308	19971113 <--
EP 941112	B1	20030212		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
IN 183279	A	19991030	IN 1997-CA2150	19971113 <--
CN 1239435	A	19991222	CN 1997-180249	19971113 <--
BR 9712947	A	20000328	BR 1997-12947	19971113 <--
JP 2001503777	T2	20010321	JP 1998-522866	19971113 <--
AT 232395	E	20030215	AT 1997-948308	19971113 <--
ES 2187832	T3	20030616	ES 1997-948308	19971113 <--

PRIORITY APPLN. INFO.: US 1996-748448 A 19961113
WO 1997-US20867 W 19971113
OTHER SOURCE(S): MARPAT 129:27894
GI



I

AB RZXCOCHR1NR2COCOR3 [R = (CH2)mAr or (CH2)mNR4R5; R1-R3 = alkyl or (hetero)aryl; R1R2 = atoms to complete a ring; R4,R5 = H, alkyl, (hetero)arylmethyl; NR4R5 = heterocyclyl; Ar = (hetero)aryl; Z =

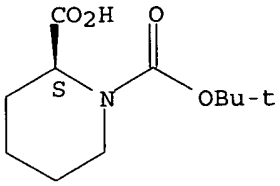
5,6,7-(un)substituted 1,2,3,4-tetrahydro-1,2-naphthylene; m = 1-3] were prepared as neurotrophic factor adjuncts for stimulation of neurite outgrowth (no data). Thus, 7-hydroxy-1-tetralone was etherified by 4-picolyl chloride and the reduced product esterified by (S)-1-allyloxycarbonylpiperidine-2-carboxylic acid to give, after deprotection, N-acylation, and resolution, title compds. (R)- and (S)-I.

IT **26250-84-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 1-tetralyl 1-oxoaracetylpiperidine-2-carboxylates and analogs as neurotrophic factor adjuncts)

RN 26250-84-0 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 45 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:116055 HCAPLUS
DOCUMENT NUMBER: 128:145376
TITLE: Antiendothelin cyclic peptide composition for prophylaxis or treatment of cerebral infarction
INVENTOR(S): Imamoto, Tetsuji; Nagisa, Yasutaka
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

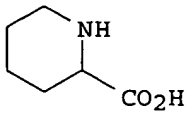
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 815870	A2	19980107	EP 1997-110271	19970624 <--
EP 815870	A3	20000503		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6251861	B1	20010626	US 1997-881878	19970624 <--
CA 2209006	AA	19971227	CA 1997-2209006	19970626 <--
JP 10072363	A2	19980317	JP 1997-170083	19970626 <--
PRIORITY APPLN. INFO.:			JP 1996-167507 A	19960627

OTHER SOURCE(S): MARPAT 128:145376

AB A pharmaceutical composition comprising a cyclic peptide having antiendothelin activity is useful for the prophylaxis or treatment of cerebral infarction.

IT **535-75-1**, Piperidine-2-carboxylic acid
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiendothelin cyclic peptide composition for prophylaxis or treatment of

cerebral infarction)
RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



L36 ANSWER 46 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:17977 HCAPLUS
DOCUMENT NUMBER: 128:70783
TITLE: **Pipecolic** acid derivative inhibitors of rotamase enzyme activity effective at stimulating neuronal growth
INVENTOR(S): Steiner, Joseph P.; Snyder, Solomon; Hamilton, Gregory S.
PATENT ASSIGNEE(S): GPI NIL Holdings, Inc., USA; Johns Hopkins Univ. School of Medicine
SOURCE: U.S., 47 pp., Cont.-in-part of U.S. Ser. No. 474,072. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5696135	A	19971209	US 1996-653905	19960528 <--
US 5798355	A	19980825	US 1995-474072	19950607 <--
CA 2206824	AA	19961219	CA 1996-2206824	19960605 <--
CA 2206824	C	20010814		
WO 9640140	A1	19961219	WO 1996-US9561	19960605 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9661622	A1	19961230	AU 1996-61622	19960605 <--
AU 710423	B2	19990923		
GB 2305605	A1	19970416	GB 1996-24258	19960605 <--
GB 2305605	B2	20000112		
DE 19680255	T	19970605	DE 1996-19680255	19960605 <--
EP 777478	A1	19970611	EP 1996-919227	19960605 <--
EP 777478	B1	20011107		
R: BE, FR, GR, IE, IT, MC, NL				
CN 1187127	A	19980708	CN 1996-194555	19960605 <--
CH 689541	A	19990615	CH 1996-2789	19960605 <--
BR 9608485	A	19990706	BR 1996-8485	19960605 <--
ES 2138518	A1	20000101	ES 1996-50031	19960605 <--
ES 2138518	B1	20010101		
NZ 310767	A	20001124	NZ 1996-310767	19960605 <--
ES 2166740	A1	20020416	ES 2000-200050035	19960605 <--
ES 2166740	B1	20031101		
FI 9604137	A	19970115	FI 1996-4137	19961015 <--
TW 523410	B	20030311	TW 1996-85113075	19961024 <--

ZA 9608981	A	19980525	ZA 1996-8981	19961025 <--
SE 9604097	A	19961208	SE 1996-4097	19961108 <--
DK 9601256	A	19961220	DK 1996-1256	19961108 <--
US 5843960	A	19981201	US 1997-787162	19970123 <--
US 5846981	A	19981208	US 1997-787163	19970123 <--
NO 9704290	A	19971204	NO 1997-4290	19970917 <--
LT 4516	B	19990625	LT 1998-2	19980106 <--
LV 11986	B	19980920	LV 1997-244	19980202 <--
ES 2194596	A1	20031116	ES 2001-200150041	19980605 <--
ES 2194596	B1	20050216		
US 6022878	A	20000208	US 1998-113330	19980710 <--
HK 1013254	A1	20000616	HK 1998-114579	19981222 <--
AU 9948793	A1	19991125	AU 1999-48793	19990916 <--
AU 740089	B2	20011101		
US 2002052372	A1	20020502	US 1999-435323	19991105 <--
US 2003114365	A1	20030619	US 2002-228312	20020827 <--

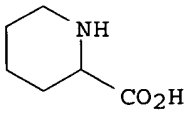
PRIORITY APPLN. INFO.:

US 1995-474072	A2	19950607
US 1996-653905	A	19960528
AU 1996-61622	A3	19960605
WO 1996-US9561	W	19960605
US 1997-787162	A1	19970123
US 1998-113330	A1	19980710
US 1999-435323	A3	19991105

AB A method is disclosed for using neurotrophic **pipecolic** acid derivative compds. having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or promote neuronal growth or regeneration. The compds. of the invention are useful for treatment of neurol. disorders.

IT **535-75-1D**, **Pipecolic** acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pipecolic** acid derivative inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and treating neurol. disorders)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



IT **130939-66-1**, **Neurotrophin** 3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pipecolic** acid derivative inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and treating neurol. disorders, and use with neurotrophic factors)

RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L36 ANSWER 47 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:489940 HCAPLUS

TITLE: In vitro and in vivo neurotrophic effects of (N-sulfonyl)- and (N-carbamoyl) **pipecolate** esters
AUTHOR(S): Li, J. -H.; Hamilton, G. S.; Huang, W.; Li, J. -H.; Connolly, M. A.; Ross, D. T.; Guo, H.; Valentine, H. L.; Steiner, J. P.
CORPORATE SOURCE: Dept. Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (**1997**), MEDI-183. American Chemical Society: Washington, D. C. CODEN: 64RNAO
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB As part of our ongoing efforts to explore the utility of a variety of FKBP12 ligands as small mol. nerve regenerating agents agents, we have synthesized several (N-sulfonyl)- and (N-carbamoyl) **pipecolate** esters and evaluated their in vitro and in vivo neurotrophic effects. Compds. which bound to FKBP12 potently elicited neurite outgrowth from sensory neuronal cultures, and restored striatal dopaminergic innervation in a mouse model of **Parkinson**'s Disease. These results further demonstrate the powerful utility of FKBP12 ligands as therapeutic agents in models of **neurodegenerative** disease.

L36 ANSWER 48 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:489939 HCAPLUS
TITLE: (N-glyoxyl) **pipecolate** esters are potent neurotrophic agents in vitro and promote recovery in a mouse model of **Parkinson**'s Disease
AUTHOR(S): Hamilton, G. S.; Huang, W.; Li, J. -H.; Connolly, M. A.; Ross, D.T.; Guo, H.; Valentine, H. L.; Steiner, J. P.
CORPORATE SOURCE: Dept. Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (**1997**), MEDI-182. American Chemical Society: Washington, D. C. CODEN: 64RNAO
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The immunophilins are "receptors" for immunosupressant drugs such as FK506 and cyclosporin A. Recently it has been discovered that the immunophilin FKBP12, which binds FK506, is enriched 10-40 fold more in the brain than in the immune tissues. Immunosuppressant drugs such as FK506 have been shown to promote neuronal process extension in vitro and regrowth of damaged peripheral nerves in vivo. It has recently been demonstrated that nonimmunosuppressive analogs of these drugs A series of simple N-(glyoxyl) **pipecolate** esters was synthesized as mimics of the FKBP12-binding domain portion of FK506. Compds. which were effective inhibitors of the prolyl isomerase activity of FKBP12 were extraordinarily potent neurotrophic agents in vitro, and were effective in a mouse model of **Parkinson**'s Disease. These results suggest that FKBP12 ligands have therapeutic utility in **neurodegenerative** diseases.

L36 ANSWER 49 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:489801 HCAPLUS
TITLE: (N-glyoxyl) **pipecolate** esters are potent neurotrophic agents in vitro and promote recovery in a mouse model of **Parkinson**'s Disease
AUTHOR(S): Hamilton, G. S.; Huang, W.; Li, J. -H.; Connolly, M.

A.; Ross, D. T.; Guo, H.; Valentine, H. L.; Steiner, J. P.
CORPORATE SOURCE: Dept. Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (**1997**), MEDI-042. American Chemical Society: Washington, D. C.
CODEN: 64RNAO
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The immunophilins are "receptors" for immunosupressant drugs such as FK506 and cyclosporin A. Recently it has been discovered that the immunophilin FKBP12, which binds FK506, is enriched 10-40 fold more in the brain than in the immune tissues. Immunosuppressant drugs such as FK506 have been shown to promote neuronal process extension in vitro and regrowth of damaged peripheral nerves in vivo. It has recently been demonstrated that nonimmunosuppressive analogs of these drugs A series of simple N-(glyoxyl) **pipecolate** esters was synthesized as mimics of the FKBP12-binding domain portion of FK506. Compds. which were effective inhibitors of the prolyl isomerase activity of FKBP12 were extraordinarily potent neurotrophic agents in vitro, and were effective in a mouse model of **Parkinson**'s Disease. These results suggest that FKBP12 ligands have therapeutic utility in **neurodegenerative** diseases.

L36 ANSWER 50 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:469003 HCAPLUS
DOCUMENT NUMBER: 127:185374
TITLE: FKBP12-binding domain analogs of FK506 are potent, nonimmunosuppressive neurotrophic agents in vitro and promote recovery in a mouse model of Parkinson's disease
AUTHOR(S): Hamilton, G. S.; Huang, W.; Connolly, M. A.; Ross, D. T.; Guo, H.; Valentine, H. L.; Suzdak, P. D.; Steiner, J. P.
CORPORATE SOURCE: Guilford Pharmaceuticals, Inc., Dept. Of Research, Baltimore, MD, 21224, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1997**), 7(13), 1785-1790
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of simple N-(glyoxyl)**pipecolate** esters were synthesized (by known methods) as mimics of the FKBP12-binding domain portion of FK506. Compds. which were effective inhibitors of the prolyl isomerase activity of FKBP12 were extraordinarily potent neurotrophic agents in vitro, and were effective in a mouse model of **Parkinson**'s Disease. These results suggest that FKBP12 ligands have therapeutic utility in **neurodegenerative** diseases.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 51 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:397372 HCAPLUS
DOCUMENT NUMBER: 127:13470
TITLE: Neurotrophic **pipecolic** acid derivs. as rotamase inhibitors for treatment of **neurodegenerative** disorders
INVENTOR(S): Steiner, Joseph P.; Hamilton, Gregory S.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA

SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9716190	A1	19970509	WO 1996-US13624	19960826 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 2002013344	A1	20020131	US 1995-551026	19951031 <--
US 5801197	A	19980901	US 1996-645149	19960513 <--
AU 9668573	A1	19970522	AU 1996-68573	19960826 <--
AU 713302	B2	19991125		
EP 859614	A1	19980826	EP 1996-929014	19960826 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI				
JP 11514643	T2	19991214	JP 1996-517308	19960826 <--
ZA 9608982	A	19980907	ZA 1996-8982	19961025 <--
NO 9801903	A	19980630	NO 1998-1903	19980427 <--

PRIORITY APPLN. INFO.:

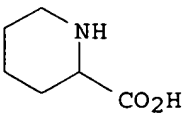
US 1995-551026	A	19951031
US 1996-645149	A	19960513
WO 1996-US13624	W	19960826

OTHER SOURCE(S): MARPAT 127:13470

AB A method is disclosed of using specially formulated neurotrophic **pipecolic** acid derivs. (Markush included) having an affinity for FKBP-type immunophilins as inhibitors of rotamase enzyme activity to stimulate or promote neuronal growth or regeneration. The compds. of the invention may be used in treatment of **neurodegenerative** disorders , e.g. **Alzheimer**'s disease, **Parkinson**'s disease, and other **neuropathies.**

IT **535-75-1D**, **Pipecolic** acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurotrophic **pipecolic** acid derivs. as rotamase inhibitors for treatment of **neurodegenerative** disorders)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



IT **130939-66-1**, **neurotrophin** 3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurotrophic **pipecolic** acid derivs. as rotamase inhibitors for treatment of **neurodegenerative** disorders in combination with neurotrophic factors)

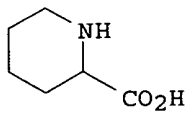
RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L36 ANSWER 52 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:165074 HCAPLUS
DOCUMENT NUMBER: 126:152815
TITLE: Rotamase inhibitors for treatment of neurological diseases
INVENTOR(S): Steiner, Joseph P.; Synder, Solomon; Hamilton, Gregory S.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals, Inc., USA; Johns Hopkins University School of Medicine
SOURCE: Jpn. Kokai Tokkyo Koho, 41 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08333256	A2	19961217	JP 1996-132866	19960430 <--
JP 3060373	B2	20000710		
US 5798355	A	19980825	US 1995-474072	19950607 <--
CN 1187127	A	19980708	CN 1996-194555	19960605 <--
LT 4516	B	19990625	LT 1998-2	19980106 <--

PRIORITY APPLN. INFO.: US 1995-474072 A 19950607
AB Rotamase or peptidyl-prolyl isomerase inhibitors e.g. neurotrophic **pipecolinic** acid derivs. (including FK506, Way 124666, Rapamycin, SLB 506, etc.) with FKBP-type immunophilin affinity are claimed for stimulating nerve growth and regeneration after nerve injury in treatment of neurol. diseases e.g. **Alzheimer**'s disease, **parkinsonism**, muscle atrophy, etc. The effects of these inhibitors were comparable to that of nerve growth factor.
IT **535-75-1D**, **Pipecolinic** acid, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rotamase inhibitors for treatment of neurol. diseases)
RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



L36 ANSWER 53 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:151523 HCAPLUS
DOCUMENT NUMBER: 126:152817
TITLE: **Pipecolic** acid derivatives as inhibitors of rotamase activity, and use in treatment of nervous system disorders.
INVENTOR(S): Steiner, Joseph P.; Snyder, Solomon; Hamilton, Gregory S.

PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA; Johns Hopkins University School of Medicine
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640140	A1	19961219	WO 1996-US9561	19960605 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5798355	A	19980825	US 1995-474072	19950607 <--
US 5696135	A	19971209	US 1996-653905	19960528 <--
AU 9661622	A1	19961230	AU 1996-61622	19960605 <--
AU 710423	B2	19990923		
GB 2305605	A1	19970416	GB 1996-24258	19960605 <--
GB 2305605	B2	20000112		
DE 19680255	T	19970605	DE 1996-19680255	19960605 <--
EP 777478	A1	19970611	EP 1996-919227	19960605 <--
EP 777478	B1	20011107		
R: BE, FR, GR, IE, IT, MC, NL				
BR 9608485	A	19990706	BR 1996-8485	19960605 <--
NZ 310767	A	20001124	NZ 1996-310767	19960605 <--
FI 9604137	A	19970115	FI 1996-4137	19961015 <--
TW 523410	B	20030311	TW 1996-85113075	19961024 <--
SE 9604097	A	19961208	SE 1996-4097	19961108 <--
DK 9601256	A	19961220	DK 1996-1256	19961108 <--
NO 9704290	A	19971204	NO 1997-4290	19970917 <--
HK 1013254	A1	20000616	HK 1998-114579	19981222 <--

PRIORITY APPLN. INFO.:			
US 1995-474072	A	19950607	
US 1996-653905	A	19960528	
WO 1996-US9561	W	19960605	

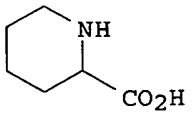
AB Neurotrophic **pipecolic** acid derivs. having an affinity for FKBP-type immunophilins are useful as inhibitors of the enzyme activity associated with immunophilin proteins, and in particular inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity, to stimulate or promote neuronal growth or regeneration. The compds, of the invention (e.g. Way-124,666; SLB-506) are useful for the treatment of neurol. disorders. The compds. may be used in conjunction with a neurotrophic factor (neurotrophic growth factor, brain-derived growth factor, **neurotrophin**-3, etc.).

IT **130939-66-1**, **neurotrophin**-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pipecolic** acid derivs. as inhibitors of rotamase activity, and use in combination with neurotrophic factor in treatment of nervous system disorders.)

RN 130939-66-1 HCAPLUS
CN Neurotrophin 3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **535-75-1D**, **Pipecolic** acid, derivs.

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pipecolic** acid derivs. as inhibitors of rotamase activity, and use in treatment of nervous system disorders.)
RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



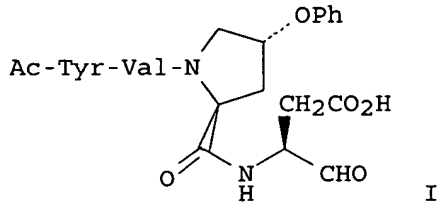
L36 ANSWER 54 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:214750 HCAPLUS
DOCUMENT NUMBER: 124:290273
TITLE: Preparation of peptide analogs as inhibitors of interleukin-1 beta converting enzyme (ICE)
INVENTOR(S): Bemis, Guy W.; Golec, Julian M. C.; Lauffer, David J.; Mullican, Michael D.; Murcko, Mark A.; Livingston, David J.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorp., USA
SOURCE: PCT Int. Appl., 374 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9535308	A1	19951228	WO 1995-US7617	19950616 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5756466	A	19980526	US 1994-261452	19940617 <--
US 5656627	A	19970812	US 1995-405581	19950317 <--
US 5847135	A	19981208	US 1995-440898	19950525 <--
AU 9529446	A1	19960115	AU 1995-29446	19950616 <--
AU 709114	B2	19990819		
EP 784628	A1	19970723	EP 1995-925257	19950616 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9508051	A	19971021	BR 1995-8051	19950616 <--
JP 10504285	T2	19980428	JP 1996-502478	19950616 <--
AP 797	A	20000107	AP 1997-960	19950616 <--
W: KE, MW, SD, SZ, UG				
PL 185693	B1	20030731	PL 1995-318220	19950616 <--
RU 2242480	C2	20041220	RU 1997-100937	19950616
NO 9605365	A	19970217	NO 1996-5365	19961213 <--
NO 317947	B1	20050110		
FI 9605036	A	19970214	FI 1996-5036	19961216 <--
BG 63634	B1	20020731	BG 1997-101130	19970114 <--
US 6420522	B1	20020716	US 1999-430822	19991029 <--

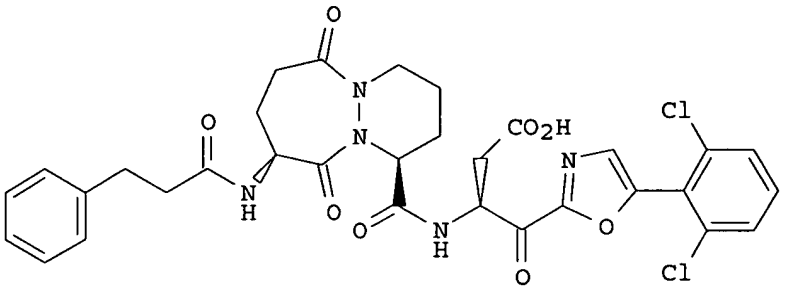
PRIORITY APPLN. INFO.: US 1994-261452 A 19940617
US 1995-405581 A 19950317
US 1995-440898 A 19950525
US 1995-465216 A3 19950605
WO 1995-US7617 W 19950616

OTHER SOURCE(S): MARPAT 124:290273

GI



I



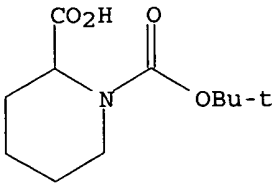
II

AB Novel classes of compds. are prepared, which are characterized by specific structural and physicochem. features comprising (a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE selected from the carbonyl O and the amide NH group of Arg-341 Ser-339, (b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a sep. binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected form the P2, P3, P4, and P' binding pockets, and (c) an electroneg. moiety comprising ≥1 electroneg. atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming ≥1 hydrogen bonds or salts bridges with residues in the P1 binding pocket of ICE. These compds. and pharmaceutical compns. of this invention are particularly well suited for inhibiting ICE activity and consequently may be advantageously used as agents against interleukin-1 mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. Thus, etherification of Me N-tert-butoxycarbonyl-cis-4-hydroxyprolinate with phenol using Ph3P and di-Et azodicarboxylate in THF to Me N-tert-butoxycarbonyl-cis-4-phenoxyprolinate followed by deprotection with HCl in EtOAc to Me 4-phenoxyprolinate hydrochloride and condensation with Ac-Tyr-Val-OH using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBT, and diisopropylethylamine in DMF gave Me N-acetyl-L-tyrosinyl-L-valyl-(4-phenoxy)prolinate. Saponification of the latter peptide ester with LiOH in aqueous THF to N-acetyl-L-tyrosinyl-L-valyl-(phenoxy)proline followed by condensation with N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran gave N-[N-acetyl-L-tyrosinyl-L-valyl-(4-phenoxy)prolinyl]-4-amino-5-benzyloxy-2-oxotetrahydrofuran (1:1 diastereomer mixture), which underwent hydrogenolysis over Pd(OH)2 in MeOH

under H atmospheric to give the title compound (I). In a IL-1β assay with a mixed population of human peripheral blood mononuclear cells or enriched adherent mononuclear cells, I in vitro showed IC50 of 2.6 and 0.25 μM for inhibiting the processing of pre-IL-1β by ICE.

IT **98303-20-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptide analogs as inhibitors of interleukin-1 beta converting enzyme for treating inflammatory, autoimmune and **neurodegenerative** diseases)

RN 98303-20-9 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



L36 ANSWER 55 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:385993 HCAPLUS
DOCUMENT NUMBER: 122:214531
TITLE: Preparation of novel cyclic pentapeptides as endothelin antagonists
INVENTOR(S): Ishikawa, Kiyofumi; Fukami, Takehiro; Ihara, Masaki; Nishikibe, Masaru; Yano, Mitsuo
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9418235	A1	19940818	WO 1994-JP151		19940202	<--
W: AU, CA, US						
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE						
AU 9459785	A1	19940829	AU 1994-59785		19940202	<--
JP 07089993	A2	19950404	JP 1994-29161		19940202	<--
PRIORITY APPLN. INFO.:			JP 1993-40450	A	19930204	
			JP 1993-168638	A	19930615	
			WO 1994-JP151	W	19940202	

OTHER SOURCE(S): MARPAT 122:214531
AB Cyclic pentapeptides represented by the general formula cyclo (-X1-X2-X3-X4-X5-) [I; X1 = D-Trp(2-F), D-Trp(2-Br), D-Trp(2-Cl), D-Trp(2-I), D-Trp(2-Me); X2 = D-Asp, D-Asp(OMe), D-Glu, D-Cys(O3H); X3 = Pro, Hyp, L-**pipecolic** acid (Pip), L-thiazolidine-4-carboxylic acid (Thz), N-(un)substituted C1-6 alkyl- or C3-7 cycloalkyl-(un)substituted Gly, Ala, L-α-aminobutyric acid (α-Aba), 2-amino-2-methylpropionic acid (Aib), Val, L-norvaline (Nva), Leu, Ile, allo-isoleucine (aIle), Nle, D-2-cyclopropylglycine (Cprg), D-2-cyclopentylglycine (Cpeg), D-2-cyclohexylglycine (Chg),L-2-cyclopropylalanine (Cpra), L-2-cyclopentylalanine (Cpea),

L-2-cyclohexylalanine (Cha), Met, etc.; X4 = D-Ala, D-α-Aba, D-Val, D-Nva, D-Leu, D-Ile, D-aIle, D-Nle, D-2-amino-3,3-dimethylbutyric acid (D-tert-Leu), etc.; X5 = N-C1-6 alkyl-(un)substituted Ala, α-Aba, Val, Nva, Leu, Ile, aIle, Nle, γ-methyl-D-leucine (γ-MeLeu), Met, L-phenylglycine (Phg), L-2-(2-thienyl)glycine (Thg), etc.] and a pharmaceutically acceptable salt thereof are prepared The peptides I have high affinity to endothelin receptor subtype ETA and ETB, show vasodilating and bronchodilating activity by inhibiting the activity of endothelin, and are useful for preventing and treating various diseases related to endothelin such as hypertension, pulmonary hypertension, Raynaud's disease, acute kidney failure, myocardial **infarction**, angina pectoris, **cerebral infarction**, cerebral vascular atrophy, **arteriosclerosis**, asthma, **diabetes**, stomach ulcer, endotoxin shock, etc. Thus, cyclo[D-Trp(2-Br)-D-Asp-Pro-D-tert-Leu-Leu] was prepared by the solution method using N-Boc-protected amino acids and in vitro inhibited the binding of 125I-endothelin to endothelin ETA receptor preparation from pig aorta smooth muscle tissue and endothelin ETB receptor preparation from pig cerebellum by 97 and 100%, resp.

L36 ANSWER 56 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:245789 HCAPLUS
DOCUMENT NUMBER: 120:245789
TITLE: Preparation of cyclic pentapeptides as endothelin receptor (ETB) antagonists
INVENTOR(S): Ishikawa, Kyobumi; Fukami, Takehiro; Ihara, Masaki; Yano, Mitsuo
PATENT ASSIGNEE(S): Banyu Pharma Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05279390	A2	19931026	JP 1993-27289	19930122 <--
PRIORITY APPLN. INFO.:			JP 1992-56249 A1	19920206

OTHER SOURCE(S): MARPAT 120:245789
AB Cyclo(-X1-X2-X3-X4-X5-) [I; X1 = D-Trp, D-Trp(CO2R), D-Trp(OR), wherein R = C1-6 alkyl; X2 = D-Asp, D-, L-, or DL-aminomalonic acid residue (Ama) optionally substituted by C1-6 alkyl at α-position; X3 = Pro, 4-hydroxy-L-proline (Hyp), L-**pipecolic** acid (Pip), L-thiazoline-4-carboxylic acid (Thz), optionally N-(imidazolyl-, CO2H-, SO3H-, or HO-substituted) C1-6 alkyl- or C3-7 cycloalkyl-substituted Gly, Ala, L-α-aminobutanoic acid (αAba), 2-amino-2-methylpropionic acid (Aib), Val, norvaline (NVa), Leu, Ile, alloisoleucine (aIle), norleucine (Nle), Met, Met(O), Met(O2), Phe, L-3-(2-thiazolyl)alanine (Tza), L-3-(2-thienyl)alanine (Tha), Tyr, Trp, His, Arg, Lys, Lys(CHO), Orn, Orn(CHO), Asn, Gln, Asp, Glu, L-cysteic acid [Cys(O3H)], Cys, Ser, or Thr; X4 = D-Val, D-Ile, D-aIle, D-2-amino-3,3-dimethylbutanoic acid (D-tert-Leu), D-2-cyclopentylglycine (D-Cpeg), D-2-cyclohexylglycine (D-Chg), D-penicillamine (D-Pen), 1-aminocyclohexanecarboxylic acid (Ac6c); X5 = Val, Leu, Ile, aIle, Cprg, Cpeg, Chg, L-2-cyclopropylalanine (Cpra), L-2-cyclopentylalanine (Cpea), L-2-cyclohexylalanine (Cha), γ-MeLeu] are prepared Medicaments for the treatment of hypertension, lung hypertension, Raynaud's disease, acute kidney failure, myocardial **infarction**, angina pectoris, **cerebral infarction**, atrophy of brain blood vessels, **arteriosclerosis**, bronchial asthma, stomach ulcer, endotoxin shock, multi-organ failure caused by

endotoxin, disseminated intravascular agglutination, and/or cyclosporin-induced kidney disorders and hypertension contain I or pharmacol. acceptable salts. H-D-Trp-D-Asp(OCMe3)-Pro-D-tert-Leu-γMeLeu-HMP resin (prepared by a peptide synthesizer Applied Biosystems model 432A using the standard Fmoc cycle) was treated with 10% hydrazine hydrate solution in DMF at room temperature to give H-D-Trp-D-Asp(OCMe3)-Pro-D-tert-Leu-(γ-Me)Leu-NHNH2. A solution of the latter hydrazide (84 mg) in DMF was treated with a solution of 3.78N HCl in dioxane at -70° and then isoamyl nitrite at -30°; after stirring at -30 to -20°, the reaction solution was cooled to -70°, diluted with DMF , adjusted to pH 7 by adding Et3N, and stirred at -20° overnight to give cyclo(-D-Trp-D-Asp(OCMe3)-Pro-D-tert-Leu-(γ-Me)Leu-). The latter cyclopentapeptide was reacted with ClCO2Me in CH2Cl2 containing NaOH and Bu4N+HSO4- under ice-cooling to give cyclo(-D-Trp-D-Asp(CO2Me)-Pro-D-tert-Leu-(γ-Me)Leu-) (II). II in vitro inhibited the binding of 125I-endothelin-1 to EtB receptor preparation from homogenized porcine cerebellum by 90%.

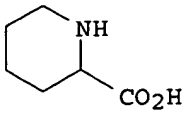
L36 ANSWER 57 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:120907 HCAPLUS
DOCUMENT NUMBER: 116:120907
TITLE: Pharmaceuticals containing 1,4-diazabicyclo[4.4.0]decane-5-one for activating and protecting cerebral metabolism and improving cerebral function
INVENTOR(S): Yamamoto, Junji; Arima, Takashi; Kasahara, Nobuo; Kajitani, Akira; Kawaguchi, Akihiro; Sato, Atsushi
PATENT ASSIGNEE(S): Taiho Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03258720	A2	19911119	JP 1990-56958	19900308 <--
PRIORITY APPLN. INFO.:			JP 1990-56958	19900308

AB Pharmaceuticals for activating and protecting cerebral metabolism and improving cerebral function, contain 1,4-diazabicyclo[4.4.0]decane-5-one (I) as an active ingredient, which shows antiamnesia and antianoxia activities, and low toxicity, and is useful for treatment of **senile dementia.** Et N-(2-phthalimidylethyl) **pipecolate** (preparation given; 300 g) and 50 g hydrazine monohydrate were dissolved in EtOH and refluxed for 1 h to give 104 g I (yield 74%). I at 30 mg/kg p.o. increased the latent time in a step-through type passive avoidance learning test in rats by 832%, vs. 230% for aniracetam. I at 100 and 300 mg/kg p.o. increased survival time by 61 and 71%, resp., in an antianoxia action test in rats, vs. 26 and 23% for aniracetam. LD50 of I was ≥2000 mg/kg p.o. in mice. A tablet was prepared from I 100, lactose 85, fine crystalline cellulose 50, hydroxypropyl starch 30, talc 4, and Mg stearate 1 mg.

IT **535-75-1, Pipecolic** acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ethanol and hydrogen chloride)

RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



L36 ANSWER 58 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:164815 HCAPLUS
DOCUMENT NUMBER: 114:164815
TITLE: Preparation of peptides as antidementia agents
INVENTOR(S): Masaki, Mitsuo; Uehara, Masaki; Hirate, Kenji; Isowa, Yoshikazu; Sato, Yoshiaki; Nakashima, Yoshiharu
PATENT ASSIGNEE(S): Nippon Chemiphar Co., Ltd., Japan; Fujirebio, Inc.
SOURCE: Eur. Pat. Appl., 36 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
EP 393934	A1	19901024	EP 1990-303987	19900412	<--
EP 393934	B1	19941102			
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE					
JP 02273696	A2	19901108	JP 1989-95917	19890415	<--
JP 2640778	B2	19970813			
JP 02273695	A2	19901108	JP 1989-95918	19890415	<--
JP 2542254	B2	19961009			
JP 02273697	A2	19901108	JP 1989-95919	19890415	<--
JP 08032722	B4	19960329			
JP 02273694	A2	19901108	JP 1989-95920	19890415	<--
JP 08026067	B4	19960313			
JP 02273698	A2	19901108	JP 1989-95921	19890415	<--
JP 08026069	B4	19960313			
JP 02273699	A2	19901108	JP 1989-95922	19890415	<--
JP 08026070	B4	19960313			
CA 2014590	AA	19901015	CA 1990-2014590	19900412	<--
CA 2014590	C	19991214			
EP 620230	A1	19941019	EP 1994-100233	19900412	<--
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE					
KR 155559	B1	19981015	KR 1990-5215	19900414	<--
US 5112947	A	19920512	US 1990-509950	19900416	<--
AU 9053621	A1	19901018	AU 1990-53621	19900417	<--
AU 642644	B2	19931028			
ZA 9002869	A	19910227	ZA 1990-2869	19900417	<--
US 5349050	A	19940920	US 1992-838140	19920218	<--

PRIORITY APPLN. INFO.:

JP 1989-95917	A	19890415
JP 1989-95918	A	19890415
JP 1989-95919	A	19890415
JP 1989-95920	A	19890415
JP 1989-95921	A	19890415
JP 1989-95922	A	19890415
EP 1990-303987	A3	19900412
US 1990-509950	A3	19900416

OTHER SOURCE(S): MARPAT 114:164815
GI

H-pGlu-Asn-Cys-A-B-Gly-OH
|
H-Cys-OH I

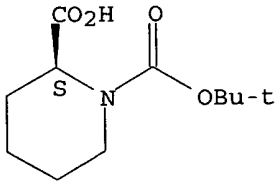
AB The title peptides [I; A = D- or L-Pro and B = citrulline (Cit) or homoarginine (Har) residue; A = D-Pro, B = Arg; A = Sar, **pipecolic** acid residue (Pip), azetidine-2-carboxylic acid (Aze), or Arg, B = D- or L-Arg], H-Asn-A-L- (or D-) Pro-Arg-(Gly)nOH (A = Ser, Thr, Ala; n = 0, 1), A-Ser-Pip-Arg-OH (A = H-Pro-Asn, H-Asn, H-Pro), A-Cys(W)-Pro-Arg-B [A = cyclopentylcarbonyl, H-Pro, H-pGlu (pGlu = pyroglutamic acid residue); B = Gly-OH, β-Ala-OH; W = H, S-linked H-Cys-OH or (A-Cys-Pro-Arg-B)2], H-pGlu-Asn-Ser-A-B-(Gly)nOH (A = Aze, D- or L-Pro, Pip, Ser; B = D- or L-Arg, Cit, Har, Lys, Orn; n = 0, 1), H-Pro-(Asn)m-Ser-L-(or D-)-Pro-Arg-(Gly)nOH (m, n = 0, 1), and H-Pro-(Asn)m-Ser-L-(or D-)-Pro-Arg-(Gly)nOH (n = 0, 1), having a nootropic effect superior to vasopressin, were prepared Approx. 30 peptides were prepared by the solution method and 8 peptides at 0.1 and 1 ng/kg showed 213-460% improvement effect on **memory** consolidation in retrograde amnesia induced by a electro-shock and cycloheximide. Injection, collunarium, and suppository formulations containing the title peptides are given.

IT **26250-84-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide coupling of, in preparation of **antidementia** peptide)

RN 26250-84-0 HCAPLUS

CN 1,2-Piperidinedicarboxylic acid, 1-(1,1-dimethylethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L36 ANSWER 59 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:632059 HCAPLUS

DOCUMENT NUMBER: 113:232059

TITLE: Preparation of acylpyroglutamates and isoxazolylalanines and analogs as biological memory enhancers

INVENTOR(S): Harada, Setsuo; Nagaoka, Akinobu; Itoh, Katsumi; Terao, Shinji

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

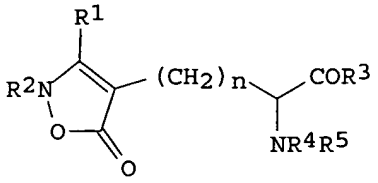
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 367393	A2	19900509	EP 1989-309430		19890918	<--
EP 367393	A3	19910327				
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE						
JP 03173864	A2	19910729	JP 1989-235123		19890911	<--
US 5021439	A	19910604	US 1989-408389		19890918	<--
PRIORITY APPLN. INFO.:			JP 1988-276919	A	19881031	
			JP 1989-95595	A	19890414	
			JP 1989-222241	A	19890829	
			JP 1989-235123	A	19890911	

OTHER SOURCE(S): MARPAT 113:232059

GI



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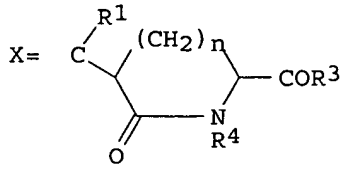
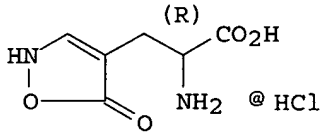


II



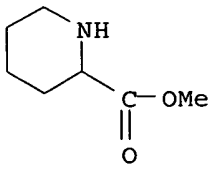
III

AB The title compds. [I and II; R1 = H, C-connected organic residue; R2 = H, protecting group; R3 = H, ester or amide residue; R4, R5 = H, acyl, (aryl-substituted) hydrocarbyl; NR4R5 = ring, (substituted) benzylidene; X = O, NOH; n = 0-3], were prepared Thus, Me (R)-N-tert-butoxycarbonylpyroglutamate in THF at -78° was treated with LiN(CHMe2)2 and then HCO2CHMe2 to give 29% II (R1 = H, R3 = OMe, R4 = Me3CO2C, X = O, n = 1). The latter was oximated and then treated successively with NaOH in MeOH, aqueous NaOH, and HCl/dioxane to give title isoxazolone III. III at 10 mg/kg i.p. in mice increased latency in a light-dark shock test from 100% (cycloheximide-impaired controls) to 278%. Tablet and injection formulations of III.Na are given.

IT **32559-18-5**, Methyl 2-piperidinecarboxylate hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of glutamate agonist-**memory** enhancer)

RN 32559-18-5 HCAPLUS

CN 2-Piperidinecarboxylic acid, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

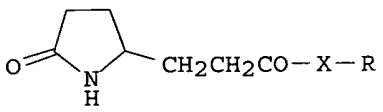


● HCl

L36 ANSWER 60 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:542379 HCAPLUS
DOCUMENT NUMBER: 103:142379
TITLE: N-[1-Oxo-3-(5-oxo-2-pyrrolidinyl)propyl] α-amino acids and derivatives as cognition activators
INVENTOR(S): Butler, Donald E.; Hershenson, Fred M.; Pavia, Michael R.
PATENT ASSIGNEE(S): Warner-Lambert Co. , USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4525476	A	19850625	US 1983-498449	19830526 <--
PRIORITY APPLN. INFO.:			US 1983-498449	19830526

OTHER SOURCE(S): MARPAT 103:142379
GI



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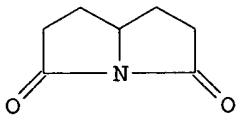
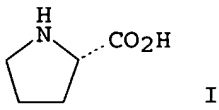


II

AB Title compds. I [X = Ala, Val, Leu, Ile, Phe, Trp, Met, Gly, Ser, Thr, Cys, Tyr, Asn, Gln, Pro, **pipecolic** acid residue; R = OH, C1-6 alkoxy, C2-6 haloalkoxy, NR1R2 (R1, R2 = H, C1-6 alkyl), OR3 (R3 = cation)] were prepared as agents for treating **senility** or amnesia. Thus, pyrrolizidinedione II was treated with H-Leu-OCMe3 in refluxing acetone for 24 h gave I (X = Leu, R = OCMe3) (III). III at 10 mg/kg (oral) produced 41% reversal of amnesia induced by electroconvulsive shock.

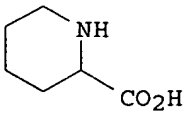
L36 ANSWER 61 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:462554 HCAPLUS
DOCUMENT NUMBER: 93:62554
TITLE: Amnestic potency of proline analogs correlates with antispreading depression potency
AUTHOR(S): Van Harreveld, Anthonie; Cherkin, Arthur; Davis, Joel L.

CORPORATE SOURCE: Div. Biol., California Inst. Technol., Pasadena, CA, 91125, USA
SOURCE: Pharmacology, Biochemistry and Behavior (**1980**), 12(4), 533-41
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



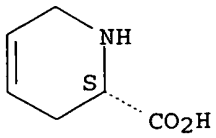
I

AB L-Proline (I) [147-85-3] and some of its analogs prevent spreading depression (SD) in the chick retina at relatively low concns. and impair **memory** processing without provoking toxic or electrophysiol. disturbances. Both effects may be caused by inhibition of the effects of glutamate released into extracellular space. I, its D-enantiomer [344-25-2], 6 proline analogs including 2 homologs (L-azetidine-2-carboxylic acid [2133-34-8] and DL-**pipecolic** acid [**4043-87-2**]), and 5 other compds. were examined for their effects on spreading depression and their amnestic and electrophysiol. effects. I, L-baikiain [**31456-71-0**], DL-3,4-dehydroproline [3395-35-5], and L-4-hydroxyproline [51-35-4] all reduced the incidence of SD in the chick retina and were amnestic. D-Proline, L-pyroglutamic acid [98-79-3], L-azetidine-2-carboxylic acid, DL-**pipecolic** acid, L-glutamic acid di-Et ester [16450-41-2], L-isoleucine [73-32-5], and L-norleucine [327-57-1] neither depressed SD nor caused retrograde amnesia. L-Prolyl-L-proline [20488-28-2] and L-glutamine [56-85-9] did not depress SD at low concns. but had amnestic effects. None of the listed compds. induced EEG disturbances. Implications for **memory** mechanisms are discussed in the light of these results.
IT **535-75-1 31456-71-0**
RL: PRP (Properties)
(eye retina spreading depression and **memory** response to)
RN 535-75-1 HCAPLUS
CN 2-Piperidinecarboxylic acid (9CI) (CA INDEX NAME)



RN 31456-71-0 HCAPLUS
CN 2-Pyridinecarboxylic acid, 1,2,3,6-tetrahydro-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L36 ANSWER 62 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1969:461202 HCAPLUS
DOCUMENT NUMBER: 71:61202
TITLE: 1-(p-Hydroxyphenyl)-2-(4-alkyl- or -aralkyl-1-piperidino)-1-propanols vasodilators
INVENTOR(S): Carron, Maurice C. E.; Carron, Claude L. C.; Bucher, Bernard P.
PATENT ASSIGNEE(S): Societe Anon. des Laboratoires Robert et Carriere
SOURCE: Fr. M., 4 pp.
CODEN: FMXXAJ
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 5733		19680226	FR 1966-77770	19660927 <--
DE 1695772			DE	
GB 1159449			GB	
US 3509164		19700428	US	19670921 <--

OTHER SOURCE(S): MARPAT 71:61202
GI For diagram(s), see printed CA Issue.
AB Title compds. (I) (R = alkyl or aralkyl), and their salts are prepared I are vasodilators, cardiotonics and hypotensors. **Pipecoline** (20 g.), 32 g. p-benzyloxy-α-bromopropiophenone and 130 ml. EtOH was refluxed 3 hrs. to give 29 g. 1-(p-benzyloxyphenyl)-2-(4-methylpiperidino)-1-propanone, (II), m. 52-4° (Et2O). II (16.85 g.) in 55 ml. EtOAc was hydrogenated at 70° under a pressure of 50 kg. in the presence of 2 g. Pd/C 10 hrs. to give 13 g. I (R = Me), (III), m. 140-5° (aqueous alc.); III.HCl m. 265°; III tartrate m. 200-2°. Other I similarly prepared were (R, m.p., and m.p. of I.HCl given): Et (IV), 70° (decomposition), 230-5°; PhCH2 (V), 110°, 238-40°. LD50 [I, mg./kg. (i.p.) and mg./kg. (oral) given]: III. tartrate, 125, -; IV.-HCl, 45, 300; V ascorbate, 150, 625. Optimum daily dose: oral 2-5 mg., parenteral 2-20 mg. I are used in arteritis, Raynaud's syndrome, **cerebrosclerosis**, **atherosclerosis**, acracyanosis and chilblains.

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=> => d stat que l39
L21           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "N-ACETYL-L-PIPECOLIC
                ACID"/CN
L22             SEL  PLU=ON  L21 1- CHEM :        3 TERMS
L23           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22
L24         382 SEA FILE=REGISTRY ABB=ON  PLU=ON  PIPECOLIC
L25        4330 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 OR PIPECOL?
L26         383 SEA FILE=REGISTRY ABB=ON  PLU=ON  NEUROTROPHIN?
L27       12485 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 OR ?NEUROTROPHIN? OR
                NEUROTROPHIC FACTOR?/CV
L28          23 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L27
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L29      137170 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NEURODEGENERAT?/CV OR
                ALZHEIMER?/CV OR PARKINSON?/CV OR (HEAD OR SPINAL)(2A)(TRAUMA
                OR INJUR?) OR HUNTINGTON?/CV OR CEREBRAL INFARCTION? OR
                MULTIPLE SCLEROSIS?/CV OR  AMYOTROPH?/CV OR ALS OR DIABET?/CV
                OR NEUROPATH?/CV
L30      465718 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "NERVE, DISEASE"/CV OR
                NERVE(2A)DISEASE OR ?NEURODEG? OR ?ALZHEIMER? OR ?PARKINS? OR
                ?HUNTINGTON? OR ?INFARCT? OR ?SCLEROSIS? OR ?DIABET? OR
                ?NEUROPATH? OR ?SENIL? OR ?DEMENTI? OR MEMORY
L32          55 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25(L)(L29 OR L30)
L33        4154 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND PD=<NOVEMBER 10, 2004

L35          68 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L32 OR L28) NOT L23
L36          62 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L35
L37         374 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "FURUKAWA SHOEI"/AU OR
                FURUKAWA S/AU
L38         121 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "NITTA ATSUMI"/AU OR NITTA
                A/AU
L39          36 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L37 AND L38) NOT (L23 OR
                L36)


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=> d ibib abs hitstr l39 1-36

L39  ANSWER 1 OF 36  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:344658  HCAPLUS
DOCUMENT NUMBER:          144:445242
TITLE:                    An analog of a dipeptide-like structure of FK506
                          increases glial cell line-derived neurotrophic factor
                          expression through cAMP response element-binding
                          protein activated by heat shock protein 90/akt
                          signaling pathway
AUTHOR(S):                Cen, Xiaobo; Nitta, Atsumi; Ohya, Shin;
                          Zhao, Yinglan; Ozawa, Naoya; Mouri, Akihiro; Ibi,
                          Daisuke; Wang, Li; Suzuki, Makiko; Saito, Kuniaki;
                          Ito, Yasutomo; Kawagoe, Tetsuya; Noda, Yukihiro; Ito,
                          Yoshihisa; Furukawa, Shoei; Nabeshima,
                          Toshitaka
CORPORATE SOURCE:         Department of Neuropsychopharmacology and Hospital
                          Pharmacy, Nagoya University Graduate School of
                          Medicine, Nagoya, 466-8560, Japan
SOURCE:                   Journal of Neuroscience (2006), 26(12), 3335-3344
                          CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER:                Society for Neuroscience
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Glial cell line-derived neurotrophic factor (GDNF) is an important
     neurotrophic factor that has therapeutic implications for
     neurodegenerative disorders.  We previously showed that leucine-isoleucine
     (Leu-Ile), an analog of a dipeptide-like structure of FK506 (tacrolimus),
     induces GDNF expression both in vivo and in vitro.  In this investigation,
     we sought to clarify the cellular mechanisms underlying the GDNF-inducing
     effect of this dipeptide.  Leu-Ile transport was investigated using
     fluorescein isothiocyanate-Leu-Ile in cultured neurons, and the results
     showed the transmembrane mobility of this dipeptide.  By liquid
     chromatog.-mass spectrometry and quartz crystal microbalance assay, we
     identified heat shock cognate protein 70 as a protein binding specifically
     to Leu-Ile, and mol. modeling showed that the ATPase domain is the
     predicted binding site.  Leu-Ile stimulated Akt phosphorylation, which was
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attenuated significantly by heat shock protein 90 (Hsp90) inhibitor geldanamycin (GA). Moreover, enhanced interaction between phosphorylated Akt and Hsp90 was detected by immunopptn. Leu-Ile elicited an increase in cAMP response element binding protein (CREB) phosphorylation, which was inhibited by GA, indicating that CREB is a downstream target of Hsp90/Akt signaling. Leu-Ile elevated the levels of GDNF mRNA and protein expression, whereas inhibition of CREB blocked such effects. Leu-Ile promoted the binding activity of phosphorylated CREB with cAMP response element. These findings show that CREB plays a key role in transcriptional regulation of GDNF expression induced by Leu-Ile. In conclusion, Leu-Ile activates Hsp90/Akt/CREB signaling, which contributes to the upregulation of GDNF expression. It may represent a novel lead compound for the treatment of dopaminergic neurons or motoneuron diseases.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:117545 HCAPLUS
DOCUMENT NUMBER: 142:196486
TITLE: Involvement of glial cell line-derived neurotrophic factor in activation processes of rodent macrophages
AUTHOR(S): Hashimoto, Manabu; **Nitta, Atsumi**; Fukumitsu, Hidefumi; Nomoto, Hiroshi; Shen, Liya; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Journal of Neuroscience Research (2005), 79(4), 476-487
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The physiol. roles of glial cell line-derived neurotrophic factor (GDNF) expressed in the microglia/macrophages of the injured spinal cord have not yet been clarified. MRNA expression of chemokines, including monocyte chemoattractant protein (MCP)-1, was evoked within 1 h after transection of the spinal cord, and GDNF mRNA expression was similarly up-regulated. Immunohistochem. anal. showed that GDNF was coexpressed with MCP-1 in the CD11b-pos. cells. Therefore, we examined further the effects of GDNF on cultured rat peritoneal macrophages. GDNF enhanced the phagocytic activity of the macrophages via GFRα-1, glycosylphosphatidylinositol-anchored specific binding site of GDNF, in a c-Ret-independent manner. The influence of autocrine and/or paracrine GDNF synthesis was evaluated by performing activation expts. using macrophages cultured from heterozygous (+/-) GDNF gene-deficient mice or wild-type (+/+) mice. There were no morphol. differences dependent on genetic types or stimulators. However, the GDNF mRNA level, but not the MCP-1 or GFRα-1 mRNA level, was substantially lower in the mutant macrophages than in the +/+ cells irresp. of stimulation with MCP-1 or lipopolysaccharide (LPS). The phagocytic activity enhanced by MCP-1 or LPS was significantly lower in the mutant cells (+/-) than in the +/+ ones, demonstrating the involvement of endogenous GDNF in the activation processes of macrophages in vitro and suggesting that not only neuroprotective function but also activation of macrophages is effected by the GDNF produced after a spinal cord injury.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:72014 HCAPLUS

DOCUMENT NUMBER: 142:353267
TITLE: Inflammation-induced GDNF improves locomotor function after spinal cord injury
AUTHOR(S): Hashimoto, Manabu; **Nitta, Atsumi**; Fukumitsu, Hidefumi; Nomoto, Hiroshi; Shen, Liya; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, USA
SOURCE: NeuroReport (2005), 16(2), 99-102
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activation of microglia/macrophages after injury occurs limitedly in the CNS, which finding may explain unsuccessful axonal regeneration. Therefore, the relationship between lipopolysaccharide (LPS)-induced inflammation and recovery of locomotor function of rats after spinal cord injury was examined High-dose LPS improved locomotor function greater than low-dose LPS, being consistent with the expression of neurotrophic factor (GDNF) in microglia/macrophages. Expts. using GDNF gene mutant mice confirmed that the increase in the GDNF mRNA level, rather than the reduction in the mRNA level of inducible NO synthase, could be correlated with the restoration activity of locomotor function. These results suggest that a higher degree of inflammation leads to a higher degree of repair of CNS injuries through GDNF produced by activated microglia/macrophages.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:818840 HCAPLUS
DOCUMENT NUMBER: 141:375048
TITLE: Hydrophobic dipeptide Leu-Ile protects against neuronal death by inducing brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis
AUTHOR(S): **Nitta, Atsumi**; Nishioka, Hirofumi; Fukumitsu, Hidefumi; Furukawa, Yoshiko; Sugiura, Haruo; Shen, Liya; **Furukawa, Shoei**
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, Japan
SOURCE: Journal of Neuroscience Research (2004), 78(2), 250-258
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated whether certain hydrophobic dipeptides, Leu-Ile, Leu-Pro, and Pro-Ile, which partially resemble the site on FK506 that binds to immunophilin, could stimulate glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) synthesis in cultured neurons and found only Leu-Ile to be an active dipeptide. Leu-Ile protected against the death of mesencephalic neurons from wild-type mice but not from mice lacking the BDNF or GDNF gene. Next, we examined the effects of i.p. or i.c.v. administration of Leu-Ile on BDNF and GDNF contents. Both types of administration increased the contents of BDNF and GDNF in the striatum of mice. Also, peripheral administration of Leu-Ile inhibited dopaminergic (DA) denervation caused by unilateral injection of 6-hydroxydopamine (6-OHDA) into the striatum of mice. The number of rotations following a methamphetamine challenge was lower in the

Leu-Ile-treated group than in the nontreated group. Next, we compared the calcineurin activity and immunosuppressant activity of Leu-Ile with those of FK506. Leu-Ile was not inhibitory toward calcineurin cellular activity in cultured neuronal cells. Furthermore, Leu-Ile did not suppress Con A (ConA)-induced synthesis/secretion of interleukin-2 by cultured spleen cells, suggesting that the immunosuppressant activity of Leu-Ile may be negligible when used as a therapeutic tool for neurodegenerative diseases.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:636574 HCAPLUS
DOCUMENT NUMBER: 141:185357
TITLE: Cyclic AMP/protein kinase A signal attenuates Ca2+-induced fibroblast growth factor-1 synthesis in rat cortical neurons
AUTHOR(S): Kinukawa, Hideki; Jikou, Takahiro; **Nitta, Atsumi**; Furukawa, Yoshiko; Hashimoto, Manabu; Fukumitsu, Hidefumi; Nomoto, Hiroshi; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University Mitahora-higashi, Gifu, Japan
SOURCE: Journal of Neuroscience Research (2004), 77(4), 487-497
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fibroblast growth factor (FGF)-1 is increased in particular brain regions after birth, suggesting an involvement of some regulatory neuronal circuits. To address the neuronal activity responsible for FGF-1 synthesis, effects of various neurotransmitter receptor activation on cellular FGF-1 content were examined using cultured rat cortical neurons. Histamine, glutamate, carbachol, serotonin or γ-aminobutyric acid (GABA) caused an increase of FGF-1 content. Because this effect was mimicked by N-methyl-D-aspartate, a glutamatergic agonist; Ca2+ ionophore; depolarization with high concentration of KCl, but was abolished in Ca2+-free medium, Ca2+ influx was thought to trigger FGF-1 synthesis. Such Ca2+-mediated enhancement of FGF-1 synthesis, however, did not occur in the presence of norepinephrine (NE), but was restored by KT-5720, an inhibitor of protein kinase A (PKA), suggesting an interplay between Ca2+-activated and cAMP/PKA signals for neuronal FGF-1 synthesis. This mechanism was proved to function in vivo by stimulation of FGF-1 expression in neurons of the cerebral cortex after intracerebral administration of propranolol, an antagonist of adrenergic β receptors. This demonstrates that FGF-1 synthesis is essentially upregulated by Ca2+ influx through excitatory neuronal activities, but such an effect is abolished by neurotransmission that evokes cAMP/PKA signals. FGF-1 produced is thought to act on establishment and maintenance of particular neuronal circuits in the brain, which may be one of the ways neurotransmitters regulate brain function.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:486885 HCAPLUS
DOCUMENT NUMBER: 141:52177
TITLE: Axonal regrowth downregulated the synthesis of glial cell line-derived neurotrophic factor in the lesioned rat sciatic nerve

AUTHOR(S): Yamada, Yoshihisa; Shimizu, Katsuji; **Nitta, Atsumi**; Soumiya, Hitomi; Fukumitsu, Hidefumi; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Neuroscience Letters (2004), 364(1), 11-15
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of axonal regeneration on de novo synthesis of glial cell line-derived neurotrophic factor (GDNF) in rat sciatic nerves was examined Transection of the sciatic nerve caused a prominent increase in the GDNF content in the distal segments within 1 wk. The high level was sustained until 4 wk in the animal model in which the nerve ends were ligated with thread (non-regeneration group); however, it was reduced to the original level within 2 or 4 wk after the transection only in the segments invaded by regenerating axons in the models in which the nerve ends were coaptated (regeneration group). Expression of both GDNF protein and mRNA was decreased with a reciprocal increase in the d. of neurofilaments, used as a marker of axonal ingrowth in distal segments of the regeneration group, suggesting that axonal contact turned off the GDNF-mediated nerve regeneration activity.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:232910 HCAPLUS
DOCUMENT NUMBER: 138:379751
TITLE: Stimulation of neurotrophin synthesis by 4-methyl catechol: an approach to the treatment of neurodegeneration
AUTHOR(S): **Furukawa, Shoei**; **Nitta, Atsumi**; Furukawa, Yoshiko
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Mitahora-higashi, Gifu, 502-8585, Japan
SOURCE: Advances in Behavioral Biology (2002), 53(Catecholamine Research), 233-236
CODEN: ADBBBW; ISSN: 0099-6246
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of 4-methylcatechol (4MC) on the synthesis of brain-derived neurotrophic factor (BDNF) in the central nervous system and its potential as a neuroprotective agent are discussed. Brain BDNF synthesis induced by 4MC may affect certain neuronal functions, which was evaluated by monitoring the expression of calbindin D-28. 4-Methylcatechol that was i.p. administered for 10 days to newborn rats elicited significant increases in calbindin D-28 immunoreactivity in the dentate granule cells, mossy fiber, CA3 stratum lucidum of the hippocampus, and certain neuronal populations in the pyriform cortex. These findings suggest that subchronic 4MC administration accelerates physiol. neuronal differentiation, probably through enhanced BDNF production
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:842987 HCAPLUS
DOCUMENT NUMBER: 138:131002
TITLE: 4-Methylcatechol stimulates phosphorylation of Trk

family neurotrophin receptors and MAP kinases in cultured rat cortical neurons

AUTHOR(S): Sometani, Ayako; Nomoto, Hiroshi; **Nitta, Atsumi**; Furukawa, Yoshiko; **Furukawa, Shoei**

CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan

SOURCE: Journal of Neuroscience Research (2002), 70(3), 335-339
CODEN: JNREDK; ISSN: 0360-4012

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effects of 4-methylcatechol (4MC), a potent stimulator of nerve growth factor and brain-derived neurotrophic factor (BDNF) synthesis, on phosphorylation of cellular mols. in cultured rat cortical neurons were examined Addition of 4MC stimulated tyrosine phosphorylation of various proteins of mol. weight from 10-300 kDa including Trks, which are high-affinity neurotrophin receptors. Moreover, 4MC enhanced the phosphorylation of serine 133 of mitogen-activated protein kinase (MAPK/ERK) in a dose-dependent manner. Pretreatment of cultures with PD98059, a selective inhibitor of MAPK kinase (MEK-1), inhibited 4MC-induced phosphorylation of ERKs, demonstrating MEK-1-mediated activation. Therefore, it seems that 4MC triggered the phosphorylation of Trks, resulting in the activation of the subsequent MAPK/ERK signal cascade, or perhaps the involvement of BDNF action as 4MC can stimulate neuronal BDNF synthesis. The phosphorylation of MAPK/ERK was unaffected, however, in the presence of cycloheximide, a protein synthesis inhibitor, and K252a, a selective inhibitor of Trks, suggesting that the effect of newly synthesized BDNF was negligible on this event, and that primary sites of 4MC actions are not limited only to Trks. These results suggest that 4MC primarily activates multiple signal transduction mols. such as tyrosine kinases, including Trks. A significant increase in the survival rate of cortical neurons in the presence of 10 or 100 nM 4MC supported this idea, because the concns. were much lower than those for stimulation of BDNF synthesis. The authors' results strongly suggest that the neurotrophic actions of 4MC found so far are mediated predominantly by direct activation of some intracellular signals including MAPK/ERK rather than by neurotrophin synthesis.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:710484 HCAPLUS

DOCUMENT NUMBER: 138:281012

TITLE: FK506 protects dopaminergic degeneration through induction of GDNF in rodent brains: new treatments on the horizon in Parkinson's disease

AUTHOR(S): **Nitta, Atsumi**; Murai, Rina; Maruyama, Keiko; **Furukawa, Shoei**

CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan

SOURCE: Advances in Behavioral Biology (2002), 51(Mapping the Progress of Alzheimer's and Parkinson's Disease), 463-467
CODEN: ADBBBW; ISSN: 0099-6246

PUBLISHER: Plenum Publishing Corp.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Parkinson's disease (PD) results from the progressive degeneration of

dopaminergic (DA) neurons that innervate the striatum. With the progression of the disease, the available pharmacotherapy, involving use of the dopamine precursor L-dopa, becomes less effective and also leads to significant side effects. Therefore, recent advances in this field have concentrated on neuroprotective therapy to rescue the dopamine neurons. Many kinds of neurotrophic factors may rescue adult and developing neurons from degeneration. A factor from a glial cell line (rat B49) was found to affect dopamine neurons in cultured neurons and was cloned and named glial cell line-derived neurotrophic factor (GDNF). GDNF can promote survival and function of dopamine neurons in vivo, both the intact rat brain and in adult DA neurons after nigrostriatal lesions. It has also been shown that GDNF is secreted in the target (striatum) and transported retrogradely to the DA cell bodies in the mesencephalon. These results suggest that GDNF may be effective for dopaminergic degeneration. Therefore, GDNF is expected to be useful as a therapeutic tool for dopaminergic neurol. disorders such as PD. However, there is an important obstacle against the therapeutic application of GDNF to PD. GDNF is a macromol. that cannot pass through the blood-brain barrier, making it difficult to deliver GDNF from the periphery to brain. This drawback may force consideration of intraventricular infusion of GDNF as therapy, although this approach involves serious tech. and/or ethical problems. Transfection of cells in vivo with the GDNF gene delivered by viral vectors and the transplantation of cells engineered to contain the normal GDNF gene may be promising approaches because a few reports demonstrate their effective protection against dopaminergic neurotoxins. However, the clin. safety of these applications has not yet been fully established. Another promising approach to use neurotrophic actions for the therapeutic purposes is the stimulation of synthesis of GDNF. FK506 is one of immunosuppressant drugs. Immunosuppression is used therapeutically for a variety of purpose. One of the most important is the treatment of patients undergoing organ transplantation. Further addnl. action in brains has been reported recently. FK506 can reduce ischemic brain damage in rats, the drug cannot protect animals against quinolinate-induced excitotoxicity. These suggest the neuroprotective effects of FK506 may involve mechanisms distinct from NMDA-mediated signaling pathways. FK506 administration diminishes neural tissue damage following middle cerebral artery occlusion in rats. FK506 derivs. provide pronounced protection against neurotoxicity elicited by the β-amyloid peptide and serum deprivation of cortical cultures. The ability of FK506 to block neurotoxicity in numerous models of important neurol. diseases may have clin. relevance. FK506 penetrates the blood-brain barrier reasonably well. In this study, we demonstrate that FK506 increases GDNF in cultured brain cells and in mouse brains, protects against dopaminergic denervation induced by neurotoxicity.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:644161 HCAPLUS
DOCUMENT NUMBER: 138:13077
TITLE: Diabetic neuropathies in brain are induced by deficiency of BDNF
AUTHOR(S): **Nitta, A.**; Murai, R.; Suzuki, N.; Ito, H.; Nomoto, H.; Katoh, G.; Furukawa, Y.; **Furukawa, S.**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Neurotoxicology and Teratology (2002), 24(5), 695-701
CODEN: NETEEC; ISSN: 0892-0362
PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Diabetes is known to be one of the risk factors for dementia; however, neuropathic changes in the brain of patients with the disease have not been completely revealed. So in the present study, the authors investigated the brain function of rats with diabetes induced by streptozotocin (STZ), one of the most commonly used animal models for diabetes. In the diabetic rats, immediately working memory performance was impaired in the Y-maze task and neuronal cytoskeleton proteins such as calbindin, synaptophysin, and syntaxin were reduced. Furthermore, morphol. observation by Golgi staining showed a decrease in the number of basal dendrites and abnormality of spine structure. Next, the authors measured the content of brain-derived neurotrophic factor (BDNF) in the diabetic brain, because BDNF is one of the essential proteins for the maintenance of neuronal functions including synapse function and neuronal transmissions. In the diabetic brains, both protein and mRNA levels of BDNF were severely reduced. These results suggest that, in diabetes, synapse dysfunction is, at least in part, caused by a failure of BDNF synthesis in the brain.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:404295 HCAPLUS
DOCUMENT NUMBER: 137:273442
TITLE: Accumulation of nerve growth factor protein at both rostral and caudal stumps in the transected rat spinal cord
AUTHOR(S): Murakami, Yutaka; **Furukawa, Shoei**; **Nitta, Atsumi**; Furukawa, Yoshiko
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Mitahora-Higashi, Gifu, 502-8585, Japan
SOURCE: Journal of the Neurological Sciences (2002), 198(1-2), 63-69
CODEN: JNSCAG; ISSN: 0022-510X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Changes in the nerve growth factor (NGF) content in the rat spinal cord during development or after traumatic spinal cord injury were examined by using a two-site enzyme immunoassay (EIA) system and an immunohistochem. technique. From embryonic day (E) 14 to postnatal day (P) 70, the spinal cord contained 200-300 pg NGF/g of wet tissue evenly in all regions tested. After complete spinal cord transection of P49 rats, the NGF level started to increase in the rostral and caudal stumps nearest to the injury site at 2 and 4 days, resp. The NGF level of the caudal side returned to the original level by 2 wk, but that of the rostral side remained high even 3 wk, after the injury. At 4 days after the injury, NGF-like immunoreactivity in both stumps was predominantly localized in the axon-like structures of the white matter and in cells morphol. resembling immune cells. These observations suggest that the NGF was transported within the spinal tracts, and that NGF secreted from immune cells that had invaded into the injured spinal cord had accumulated around the transection site. Increased NGF at the injury site may be advantageous for injured neurons and involved in mechanisms directing to axonal regeneration of the injured spinal cord.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:299874 HCAPLUS
DOCUMENT NUMBER: 137:138648
TITLE: Alterations in hippocampal GAP-43, BDNF, and L1 following sustained cerebral ischemia
AUTHOR(S): Miyake, Keiko; Yamamoto, Wataru; Tadokoro, Mina; Takagi, Norio; Sasakawa, Kyoko; **Nitta, Atsumi**; **Furukawa, Shoei**; Takeo, Satoshi
CORPORATE SOURCE: Department of Pharmacology, Tokyo University of Pharmacy and Life Science, Hachioji, 192-0392, Japan
SOURCE: Brain Research (2002), 935(1,2), 24-31
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alterations in factors involved in the regeneration of the neuronal network in the hippocampus of rats with microsphere embolism (ME) were examined Nine hundred microspheres (48 μm in diameter) were injected into the right hemisphere, and immunochem. and immunohistochem. studies on the hippocampus were performed on the seventh day thereafter. Hematoxylin-eosin staining showed progressive and severe degeneration of the hippocampus after ME. The protein levels of brain-derived neurotrophic factor (BDNF), 43-kDa growth-associated protein (GAP-43), and adhesion protein L1 (L1) in the ipsilateral hippocampus of the ME animal, determined by Western blot anal. or enzyme immunoassay, were increased, unaltered, and decreased, resp. In contrast, the immunohistochem. study showed increases in a marker of axonal sprouting GAP-43, and a neurotrophic factor BDNF, and a decrease in an adhesion mol. L1 in some areas of the hippocampal ischemic penumbra of such animals. These results suggest that some factors for regeneration of the neuronal network in the ischemic penumbra responded to sustained cerebral ischemia for a certain period, although functional network of the nerve cells in the microsphere-injected hemisphere would be unlikely established after ME.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:918561 HCAPLUS
DOCUMENT NUMBER: 136:227220
TITLE: Brain-derived neurotrophic factor alters cell migration of particular progenitors in the developing mouse cerebral cortex
AUTHOR(S): Ohmiya, Makoto; Shudai, Toshihiro; **Nitta, Atsumi**; Nomoto, Hiroshi; Furukawa, Yoshiko; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Neuroscience Letters (2002), 317(1), 21-24
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of brain-derived neurotrophic factor (BDNF) on cell migration from the ventricular zone to the cortical plate (CP) in developing mouse cerebral cortex were examined BDNF (700 ng) was injected into the brain ventricle of 13- or 14-day-old embryos (E13 or E14) after the i.p. administration of 5-bromodeoxyuridine (BrdU) to pregnant mice. BDNF injection at E13 increased the number of BrdU-pos. cells migrated into the CP until E15, and caused them to become localized in much deeper layers (V-VI) than expected (IV-V, as in the vehicle-treated mice) by postnatal day 1. However, when the injections were made at E14, BrdU-pos. cells

predominantly migrated to layers II/III irresp. of BDNF administration. These results demonstrate that BDNF affects particular progenitors at limited stages, and suggest the presence of a Reelin-independent mechanism(s) to regulate cell migration.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:812366 HCAPLUS
DOCUMENT NUMBER: 136:64637
TITLE: Transforming growth factor-β1 enhances expression of brain-derived neurotrophic factor and its receptor, TrkB, in neurons cultured from rat cerebral cortex
AUTHOR(S): Sometani, Ayako; Kataoka, Hiroshige; **Nitta, Atsumi**; Fukumitsu, Hidefumi; Nomoto, Hiroshi; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Journal of Neuroscience Research (2001), 66(3), 369-376
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of transforming growth factor (TGF)-β1 on expression of brain-derived neurotrophic factor (BDNF) and its high-affinity receptor, TrkB, in neurons cultured from the cerebral cortex of 18-day-old embryonic rats were examined BDNF mRNA was significantly increased from 24-48 h after the TGF-β1 treatment over 20 ng/mL. Accumulation of BDNF protein in the culture medium was also potentiated by TGF-β1, although the intracellular content of BDNF was nearly unchanged. The enhancement of BDNF mRNA expression was suppressed by the co-presence of decorin, a small TGF-β-binding proteoglycan that inhibits the biol. activities of TGF-βs. The mRNA expression of full-length TrkB, the bioactive high-affinity receptor for BDNF, was also upregulated after treatment with TGF-β1. These observations suggest that: (1) TGF-β1 potentiates BDNF/TrkB autocrine or local paracrine system; and (2) the neurotrophic activity of TGF-β1 is partly responsible for the BDNF induced by TGF-β1 itself. To test this latter possibility, we examined the neuronal survival activity of TGF-β1 with or without K 252a, a selective inhibitor of Trk family tyrosine kinases. TGF-β1 significantly enhanced neuronal survival, but the co-presence of K 252a completely suppressed the activity, demonstrating the involvement of Trk receptor signaling in TGF-β1-mediated neuronal survival in cultured rat cortical neurons. These results seem to be in line with recent findings by other investigators that some neurotrophic factors including BDNF require TGF-βs as a co-factor to exert their neurotrophic activities.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:599341 HCAPLUS
DOCUMENT NUMBER: 135:299071
TITLE: Administration of FGF-2 to embryonic mouse brain induces hydrocephalic brain morphology and aberrant differentiation of neurons in the postnatal cerebral cortex
AUTHOR(S): Ohmiya, Makoto; Fukumitsu, Hidefumi; **Nitta, Atsumi**; Nomoto, Hiroshi; Furukawa, Yoshiko;

Furukawa, Shoei
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Journal of Neuroscience Research (2001), 65(3), 228-235
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fibroblast growth factor-2 (FGF-2) was injected into mouse cerebral ventricles at embryonic day (E) 14 in utero and its effects on developing brain morphol. and expression of various cell- or differentiation-associated protein markers in the cerebral cortex were examined High doses of FGF-2 (200 or 300 ng) caused encephalic alternations such as deformation of the calvarium, enlargement of the ventricular spaces, and thinning of the cerebral cortex. There was no gross abnormality in the alignment of the cerebral neuronal layers, however, both cell number and cell d. of the upper layers (II/III) and the lower layers (IV-VI) of the cerebral cortex were increased. Brain-derived neurotrophic factor (BDNF), tyrosine hydroxylase, nestin, and microtubule-associated protein 2 were aberrantly or ectopically expressed in the deep areas of the cerebral cortex. A substantial number of these cells coexpressed these antigens. These observations demonstrate that a subpopulation of neurons in the cortical deep layer abnormally differentiated or partly sustained their immature state following a single administration of FGF-2 at E14. Developmental anal. of localization of BDNF-pos. cells suggested that the abnormality started around P5. Furthermore, cell migration was not affected by FGF-2 administration. FGF-2 seems to play predominant roles in the proliferation of neuronal precursors and in neuronal differentiation in the developing mouse cerebral cortex even at relatively late stages of brain neurogenesis.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:474417 HCAPLUS
DOCUMENT NUMBER: 136:209861
TITLE: Stimulation of neurotrophin synthesis by 4-methylcatechol: a promising approach for neuroprotection
AUTHOR(S): **Furukawa, Shoei**; **Nitta, Atsumi**; Furukawa, Yoshiko
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Biomedical Reviews (1999), 10, 45-54
CODEN: BMREES; ISSN: 1310-392X
PUBLISHER: Bulgarian-American Center
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Neurotrophins play a crucial role in the differentiation, maintenance, and survival of various types of peripheral and central neurons. However, the therapeutic use of neurotrophins is limited by their inability to cross the blood-brain barrier and their instability in the bloodstream. One of the promising approaches to utilize neurotrophic actions of these mols. in the therapy of neurodegenerative diseases is the stimulation of neurotrophin synthesis. Here we review the effects of 4-methylcatechol, a nonadrenergic catechol compound, on the synthesis of the neurotrophins nerve growth factor and brain-derived neurotrophic factor in the peripheral and central nervous system. The neuroprotective potential of 4-methylcatechol in animal models of neurodegenerative disorders is

discussed, and other agents that enhance neurotrophin synthesis are also mentioned.
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:439729 HCAPLUS
DOCUMENT NUMBER: 136:52232
TITLE: Difference in toxicity of β-amyloid peptide with aging in relation to nerve growth factor content in rat brain
AUTHOR(S): Fukuta, T.; **Nitta, A.**; Itoh, A.; **Furukawa, S.**; Nabeshima, T.
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, Japan
SOURCE: Journal of Neural Transmission (2001), 108(2), 221-230
CODEN: JNTRF3; ISSN: 1435-1463
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amyloid β-peptide (Aβ) is the major constituent of the senile plaques in the brains of patients with Alzheimer's disease. We have demonstrated previously that memory impairment, dysfunction of the cholinergic and dopaminergic neuronal system and morphol. degeneration are produced after the continuous infusion of Aβ into the cerebral ventricle in 8-wk-old rat. In the present study, the authors investigated the toxicity of Aβ in infant (10 days old), adult (8 wk old) and aged (20 mo old) rats in relation to nerve growth factor (NGF) content in various regions of the brain. After a 2-wk-infusion, choline acetyltransferase (ChAT) activity was significantly decreased in the hippocampus of adult, but not infant or aged rats. NGF levels in the hippocampus were increased only in adult rats. These results suggest that Aβ is toxic only in the matured adult brain, and that the mechanism of toxicity is related to NGF synthesis.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:878291 HCAPLUS
DOCUMENT NUMBER: 134:145778
TITLE: Increase in neurotrophin-3 expression followed by Purkinje cell degeneration in the adult rat cerebellum after spinal cord transection
AUTHOR(S): Kawakami, Hiroshi; **Nitta, Atsumi**; Matsuyama, Yukihiro; Kamiya, Mitsuhiro; Satake, Kotaro; Sato, Koji; Kondou, Kikuo; Iwata, Hisashi; **Furukawa, Shoei**
CORPORATE SOURCE: Department of Orthopedic Surgery, Nagoya University, Nagoya, 466-8550, Japan
SOURCE: Journal of Neuroscience Research (2000), 62(5), 668-674
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Changes in brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) contents following thoracic spinal cord transection were investigated in the cerebral cortex, hippocampus, and cerebellum of rats.

The NT-3 content became significantly elevated at 3 days after transection only in the cerebellum and gradually declined to the control level by 6 days after the injury, remaining unchanged in the cerebral cortex and hippocampus. No significant change in the BDNF content was observed in any of the regions tested. Immunohistochem. anal. showed that the labeling indicating NT-3-like immunoreactivity was intensified in both cerebellar granule and Purkinje cells 3 days after the injury. The number of Purkinje cells with aggregation of chromatin around the nuclear membrane and swelling of the cytoplasm and/or organelles gradually increased with time starting 4 days after the injury, demonstrating morphol. changes indicative of necrosis. However, no abnormal morphol. was found in cerebellar granule cells at any time examined We suggest that it is reasonable that increased NT-3 stimulated the death of Purkinje cells, because 1) the degeneration was necrosis, which is known to be accelerated by neurotrophins under certain pathol. conditions, and 2) the increase in NT-3 occurred prior to Purkinje cell degeneration. Therefore, our present results may imply that spinal cord injury-induced NT-3 accelerates injury rather than alleviates degeneration of Purkinje cells.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:285385 HCAPLUS
DOCUMENT NUMBER: 133:134681
TITLE: Dietary n-3 fatty acid deficiency decreases nerve growth factor content in rat hippocampus
AUTHOR(S): Ikemoto, Atsushi; **Nitta, Atsumi**; **Furukawa, Shoei**; Ohishi, Masayo; Nakamura, Akira; Fujii, Yoichi; Okuyama, Harumi
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Department of Biological Chemistry, Nagoya City University, Mizuhoku, Nagoya, 467-8603, Japan
SOURCE: Neuroscience Letters (2000), 285(2), 99-102
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dietary deprivation of α-linolenic acid (C18:2n-3) through 2 generations decreases the performance in operant-type brightness discrimination learning tests in rats. We examined possible correlations between nerve growth factor (NGF) content and n-3 fatty acid nutritional status in the brain. Female rats were fed a semipurified diet supplemented with safflower oil (n-3 deficient) and their offsprings were fed a diet supplemented with 3% safflower oil (Saf group) or a mixture of 2.4% safflower oil plus 0.6% Et eicosapentaenoate (Saf+EPA group) after weaning. The brain docosahexaenoic acid (C22:6n-3, DHA) content in the Saf group was less than 1/2 of that in the control Per group fed a diet supplemented with 3% perilla oil (n-3 sufficient) throughout the experiment The DHA levels in the Saf+EPA group were restored to the level in the Per group. The NGF contents in the brain hippocampus in the Saf and Saf+EPA groups were 1/2 of that in the Per group. In the brain piriform cortex the NGF content tended to be higher in the Saf and Saf+EPA groups than in the Per group. Thus, dietary n-3 fatty acid deficiency and restoration affect the NGF levels differently in different brain regions.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:778432 HCAPLUS
DOCUMENT NUMBER: 132:73540

TITLE: 4-methylcatechol increases brain-derived neurotrophic factor content and mRNA expression in cultured brain cells and in rat brain in vivo

AUTHOR(S): **Nitta, Atsumi**; Ito, Megumi; Fukumitsu, Hidefumi; Ohmiya, Makoto; Ito, Hisanori; Sometani, Ayako; Nomoto, Hiroshi; Furukawa, Yoshiko; **Furukawa, Shoei**

CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Mitahora-higashi, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 291(3), 1276-1283
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Practical use of brain-derived neurotrophic factor (BDNF) as therapy is limited by two serious problems, i.e., its inability to cross the blood-brain barrier and its instability in the blood-stream. In the present study, we investigated the effects of 4-methylcatechol (4-MC), which stimulates nerve growth factor synthesis and protects against peripheral neuropathies in rats, on BDNF content and mRNA expression in cultured brain cells and in vivo in the rat brain. 4-MC elevated BDNF content in culture media of both rat astrocytes and neurons with different dose-response relations. The increase in BDNF mRNA level was correlated with the increase in BDNF content, demonstrating that 4-MC can stimulate BDNF synthesis of both neurons and astrocytes. Then we examined the in vivo effects of 4-MC. First, we found that ventricularly administered 4-MC facilitated an increase in the BDNF content in the cerebral cortex and hippocampus in association with its diffusion into the brain parenchyma. Second, i.p. administration of 4-MC enhanced BDNF mRNA expression in the infant rat brain, in which the blood-brain has not yet fully been established. These results demonstrate that 4-MC, once delivered into the brain, can stimulate BDNF synthesis.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:641488 HCAPLUS

DOCUMENT NUMBER: 132:19177

TITLE: Induction of a physiologically active brain-derived neurotrophic factor in the infant rat brain by peripheral administration of 4-methylcatechol

AUTHOR(S): Fukumitsu, H.; Sometani, A.; Ohmiya, M.; **Nitta, A.**; Nomoto, H.; Furukawa, Y.; **Furukawa, S.**

CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, Japan

SOURCE: Neuroscience Letters (1999), 274(2), 115-118
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effects of 4-methylcatechol (4MC), a known potent stimulator of nerve growth factor (NGF) synthesis, on expression of brain-derived neurotrophic factor (BDNF) mRNA and BDNF-like immunoreactivity (BDNF-LI) was investigated in infant rat brains. A single i.p. administration of 4MC caused transient increases in the levels of BDNF mRNA and BDNF-LI in neurons of the cerebral cortex from 1 to 3 h and 3 to 12 h, resp., after the injection. Repetitive injections of 4MC to newborn rats (12-h

intervals for 10 days) caused a marked and dose-dependent elevation of the level of BDNF mRNA in the whole brain besides elevating the number of cells containing calbindin D-28 and enhancing its immunoreactive intensity in the pyriform cortex and hippocampus. These findings demonstrate that 4MC stimulates de novo synthesis of BDNF in the infant rat brain, resulting in acceleration of the developmental expression of calbindin D-28.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:450475 HCAPLUS
DOCUMENT NUMBER: 131:194504
TITLE: Brain-derived neurotrophic factor prevents neuronal cell death induced by corticosterone
AUTHOR(S): **Nitta, Atsumi**; Ohmiya, Makoto; Sometani, Ayako; Itoh, Megumi; Nomoto, Hiroshi; Furukawa, Yoshiko; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502, Japan
SOURCE: Journal of Neuroscience Research (1999), 57(2), 227-235
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Corticosterone (CORT), one of the glucocorticoids, causes neuronal damage in the hippocampus, but the mechanism(s) of action underlying its effects remains unknown. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that belongs to the neurotrophin family, affects the survival and/or differentiation of various types of neurons in vitro, and is able to antagonize neuronal death induced by various brain insults or neurotoxins in vivo. In this study, the effects of CORT on BDNF protein contents and mRNA expression were investigated in relation to neuronal survival/death of cultured rat hippocampal neurons, because the colocalization of BDNF with its receptor, TrkB, suggests that BDNF may exert its putative protective and trophic effects through an autocrine mechanism in the hippocampus. Administration of CORT accelerated the neuronal death that proceeds after serum deprivation, and simultaneously reduced the levels of BDNF mRNA and intracellular BDNF content. Exogenously added BDNF actually attenuated CORT-induced neuronal death, but not in the presence of K252a, an inhibitor of the tyrosine kinase activity of Trk family receptors. These observations suggest that CORT induces damage to hippocampal neurons, at least partly, via reducing their BDNF synthesis.
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:432618 HCAPLUS
DOCUMENT NUMBER: 131:111507
TITLE: Neuronal protection by neurotrophic factors
AUTHOR(S): **Furukawa, Shoei**; **Nitta, Atsumi**; Furukawa, Yoshiko
CORPORATE SOURCE: Lab. Mol. Biol., Gifu Pharm. Univ., Japan
SOURCE: Saishin Igaku (1999), 54(7), 1730-1736
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 13 refs., on delayed neuronal death in hippocampus and

BDNF, prevention of corticosterone-induced neuronal death with BDNF, neurotrophin production by activated T cell, and approach to nerve diseases using neurotrophic factors.

L39 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:304988 HCAPLUS
DOCUMENT NUMBER: 131:111823
TITLE: Retrograde transport of endogenous NT-3 in rat sciatic nerve
AUTHOR(S): **Nitta, Atsumi**; Jin-Nouchi, Takayoshi; Asami, Toshio; Toyoda, Kaori; Hino, Mayuko; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Keio University Symposia for Life Science and Medicine (1999), 2(Neural Development), 180-185
CODEN: KUSMF9
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To address active transport of neurotrophin, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) in the peripheral nerves, the authors examined their levels of protein and mRNA in the sciatic nerve of adult rats following transection, using enzyme immunoassays and the reverse transcription polymerase chain reaction method, resp. NT-3 protein increased 1 day after transection only in the distal segment next to the transection site and returned to the original level 2 days later. This was considered to reflect accumulation of NT-3 transported from the periphery toward the neuronal cell bodies, because the NT-3 mRNA level was not changed in any sciatic segments during the exptl. period. In contrast, an increase in BDNF protein was observed simultaneously in both distal and proximal stumps 3 days after transection. BDNF mRNA was elevated in the same stumps 1 day before, suggesting that BDNF was produced within the transected stumps. These observations demonstrate that NT-3, like NGF, is retrogradely transported in the sciatic nerve but that BDNF is not, which suggests that NT-3 plays particular roles in the conveyance of trophic signals from target organs to neurons.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:304985 HCAPLUS
DOCUMENT NUMBER: 131:111580
TITLE: Brain-derived neurotrophic factor prevents neuronal cell death induced by corticosterone
AUTHOR(S): **Furukawa, Shoei**; **Nitta, Atsumi**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Keio University Symposia for Life Science and Medicine (1999), 2(Neural Development), 159-164
CODEN: KUSMF9
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Glucocorticoids cause neuronal damage in the rat hippocampus, but the mechanism(s) of action underlying the neurodegenerative effects remain unknown. Brain-derived neurotrophic factor (BDNF), one of the neurotrophins, affects survival or differentiation of various types of neurons of the central nervous system (CNS) in culture and is known to

prevent cell death of some of these neurons induced by various CNS insults. The authors investigated the effects of corticosterone on both neuronal cell death and BDNF synthesis using cultured hippocampal neurons. Most neurons survived 3 days after removal of serum, while corticosterone induced neuronal death as early as 1 day after the addition The level of BDNF mRNA was decreased in a dose-dependent manner in the presence of corticosterone, while the β-actin mRNA level was unchanged. Intracellular BDNF content was also markedly reduced in the presence of corticosterone. These observations demonstrated that corticosterone causes a decrease in BDNF mRNA and protein in cultured hippocampal neurons. Finally, the authors found that corticosterone-induced neuronal death was significantly protected by the addition of BDNF. These observations suggest that the neurotoxic effect of corticosterone is mediated by suppression of synthesis of BDNF, which has a role in support of the survival of cultured neurons.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:246806 HCAPLUS

DOCUMENT NUMBER: 131:42997

TITLE: Microsphere embolism-induced elevation of nerve growth factor level and appearance of nerve growth factor immunoreactivity in activated T-lymphocytes in the rat brain

AUTHOR(S): Mizuma, Hideyuki; Takagi, Kaori; Miyake, Keiko; Takagi, Norio; Ishida, Kumi; Takeo, Satoshi; **Nitta, Atsumi**; Nomoto, Hiroshi; Furukawa, Yoshiko; **Furukawa, Shoei**

CORPORATE SOURCE: Department of Pharmacology, Tokyo University of Pharmacy and Life Science, Hachioji, 192-0392, Japan

SOURCE: Journal of Neuroscience Research (1999), 55(6), 749-761
CODEN: JNREDK; ISSN: 0360-4012

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Changes in nerve growth factor (NGF) level and type of cells producing NGF were investigated in the rat brain after sustained cerebral embolism. The NGF level was determined by a two-site enzyme immunoassay specific for NGF. The cerebral cortex, striatum, and hippocampus of the embolized hemisphere maximally contained 2.4-, 2.4-, and 1.7-times higher NGF levels than the corresponding regions of the non-embolized hemisphere. An increase was transiently observed for 1 wk in the cerebral cortex and striatum, whereas the increase was longer lasting, at least of 4-wk' duration, in the hippocampus. To examine the localization of NGF-like immunoreactivity (NGF-LI), the authors used a newly developed anti-NGF peptide antiserum that specifically recognized a 30-kDa mol.(s) in the hippocampal exts. or in NGF cDNA-transfected cells, suggesting that the antibody predominantly reacted with the putative NGF precursor protein(s). NGF-LI, which was localized in neurons of the normal or non-embolized hemisphere, was reduced, and on the embolized side new signals emerged in small non-neuronal cells having a round shape. These included cells with common leukocyte antigen CD45 and T-lymphocyte antigen CD3, which did not appear in the normal or non-embolized hemisphere. NGF-LI and CD3 were colocalized in a substantial number of the cells, suggesting that some activated T-lymphocytes produce NGF for neuronal regeneration after sustained cerebral embolism.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:778757 HCAPLUS
DOCUMENT NUMBER: 130:105253
TITLE: Memory facilitation and stimulation of endogenous nerve growth factor synthesis by the acetylcholine releaser PG-9
AUTHOR(S): Ghelardini, Carla; Galeotti, Nicoletta; Bartolini, Alessandro; **Furukawa, Shoei**; **Nitta, Atsumi**; Manetti, Dina; Gualtieri, Fulvio
CORPORATE SOURCE: Department of Pharmacology, University of Florence, Florence, I-50134, Italy
SOURCE: Japanese Journal of Pharmacology (1998), 78(3), 245-251
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of PG-9 (3α-tropyl 2-(p-bromophenyl)propionate), the acetylcholine releaser, on memory processes and nerve growth factor (NGF) synthesis were evaluated. In the mouse passive-avoidance test, PG-9 (10-30 mg/kg, i.p.), administered 20 min before the training session, prevented amnesia induced by both the non selective antimuscarinic drug scopolamine and the M1-selective antagonist S-(-)-ET-126. In the same exptl. conditions, PG-9 (5-20 μg per mouse, i.c.v.) was also able to prevent antimuscarine-induced amnesia, demonstrating a central localization of the activity. At the highest EDs, PG-9 did not produce any collateral symptoms as revealed by the Irwin test, and it did not modify spontaneous motility and inspection activity, as revealed by the hole-board test. PG-9 was also able to increase the amount of NGF secreted in vitro by astrocytes in a dose-dependent manner. The maximal NGF contents obtained by PG-9 were 17.6-fold of the control value. During culture, no morphol. changes were found at effective concns. of PG-9. The current work indicates the ability of PG-9 to induce beneficial effects on cognitive processes and stimulate activity of NGF synthesis in astroglial cells. Therefore, PG-9 could represent a potential useful drug able to improve the function of impaired cognitive processes.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:757634 HCAPLUS
DOCUMENT NUMBER: 130:90874
TITLE: Endogenous neurotrophin-3 is retrogradely transported in the rat sciatic nerve
AUTHOR(S): **Nitta, A.**; Ohmiya, M.; Jin-Nouchi, T.; Sometani, A.; Asami, T.; Kinukawa, H.; Fukumitsu, H.; Nomoto, H.; **Furukawa, S.**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502-8585, Japan
SOURCE: Neuroscience (Oxford) (1998), Volume Date 1999, 88(3), 679-685
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To address the active transport of neurotrophins, nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 in the peripheral nerves, the authors examined the levels of proteins and mRNAs in the sciatic nerve of adult rats following transection, using enzyme immunoassays and

reverse transcription polymerase chain reaction method, resp. Neurotrophin-3 protein increased one day after transection only in the distal segment next to the transection site and returned to the original level two days later. This was considered to reflect accumulation of neurotrophin-3 transported from the periphery toward the neuronal cell bodies, because the neurotrophin-3 mRNA level was not changed in any sciatic segments during this exptl. period. An increase in brain-derived neurotrophic factor protein was observed simultaneously in both the distal and proximal stumps three days after transection. Brain-derived neurotrophic factor mRNA was elevated in the same stumps two days after transection, suggesting that brain-derived neurotrophic factor was produced within the transected stumps. These observations demonstrate that neurotrophin-3, like nerve growth factor, is retrogradely transported in the sciatic nerve but that brain-derived neurotrophic factor is not. This suggests that neurotrophin-3 plays a role in the conveyance of trophic signals from target organs to neurons.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:168140 HCAPLUS
DOCUMENT NUMBER: 128:279219
TITLE: Simultaneous expression of brain-derived neurotrophic factor and neurotrophin-3 in cajal-retzius, subplate and ventricular progenitor cells during early development stages of the rat cerebral cortex
AUTHOR(S): Fukumitsu, H.; Furukawa, Y.; Tsusaka, M.; Kinukawa, H.; **Nitta, A.**; Nomoto, H.; Mima, T.; **Furukawa, S.**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502, Japan
SOURCE: Neuroscience (Oxford) (1998), 84(1), 115-127
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To identify production sites and action targets of neurotrophins during neurogenesis, the authors investigated immunoreactivities of neurotrophins and their tyrosine kinase receptors in the cerebral cortex of rat embryos. Two sets of ligand-receptor systems, brain-derived neurotrophic factor/TrkB and neurotrophin-3/TrkC, were expressed simultaneously in Cajal-Retzius, subplate neurons and ventricular multipotent stem cells at embryonic days 13 and 15. Intraventricular administration of brain-derived neurotrophic factor or neurotrophin-3 at embryonic day 16 markedly modulated microtubule-associated protein II and/or Hu protein expression in different ways in the cortical plate cells by embryonic day 20. These observations indicate the involvement of autocrine and/or local paracrine action of brain-derived neurotrophic factor and/or neurotrophin-3 during formation of the cerebral cortex.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 30 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:121781 HCAPLUS
DOCUMENT NUMBER: 128:225486
TITLE: Clinical potential of compounds that stimulate nerve growth factor production
AUTHOR(S): **Nitta, Atsumi**; **Furukawa, Shoei**; Nabeshima, Toshitaka
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical

University, Gifu, Japan
SOURCE: Neuroprotective Signal Transduction (1998), 95-110. Editor(s): Mattson, Mark P. Humana: Totowa, N. J. CODEN: 65RQA6
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 87 refs. The topics include nerve growth factor (NGF) synthesis pharmacol. stimulation in vivo and in vitro. The effects of idebenone, propentofylline, 4-methylcatechol, and other neurotrophins with potential clin. application are discussed.
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 31 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:15363 HCAPLUS
DOCUMENT NUMBER: 128:149906
TITLE: BDNF and NT-3 modulate expression and threonine phosphorylation of microtubule-associated protein 2 analogs, and alter their distribution in the developing rat cerebral cortex
AUTHOR(S): Fukumitsu, Hidefumi; Ohashi, Akiko; **Nitta, Atsumi**; Nomoto, Hiroshi; **Furukawa, Shoei**
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu, 502, Japan
SOURCE: Neuroscience Letters (1997), 238(3), 107-110 CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-3 on the expression of structural or synapse-associated proteins were examined in the developing rat cerebral cortex. Following ventricular administration of BDNF or NT-3 at embryonic day (E) 16, expression of microtubule-associated protein (MAP) 2 of 280 kDa was enhanced at E18 and/or E20, and threonine phosphorylation of MAP2 analogs of 120 and 66 kDa was modulated in different ways. NT-3 basically altered the distribution of MAP2 proteins at E20. These findings suggest that NT-3 and BDNF play a role in regulating production and phosphorylation of MAP2 analogs during development of the rat cerebral cortex.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:749646 HCAPLUS
DOCUMENT NUMBER: 128:44209
TITLE: Brain-derived neurotrophic factor-like immunoreactivity in the adult rat central nervous system predominantly distributed in neurons with substantial amounts of brain-derived neurotrophic factor messenger RNA or responsiveness to brain-derived neurotrophic factor
AUTHOR(S): **Furukawa, S.**; Sugihara, Y.; Iwasaki, F.; Fukumitsu, H.; **Nitta, A.**; Nomoto, H.; Furukawa, Y.
CORPORATE SOURCE: Laboratory of Molecular Biology, Gifu Pharmaceutical University, Gifu, 502, Japan
SOURCE: Neuroscience (Oxford) (1997), Volume Date 1998, 82(3), 653-670 CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Distribution of brain-derived neurotrophic factor-like immunoreactivity was investigated in the adult rat brain using two types of antibodies against peptides, V2 and V4, unique to the brain-derived neurotrophic factor. Western blot anal. showed that both antibodies specifically bound brain-derived neurotrophic factor, but not other neurotrophins, and that they recognized identical mols. of 18,000 mol. weight, but not the 14,500 mol. weight mass of mature form, in exts. from the rat hippocampus. Both antibodies recognized an identical precursor form (30,000 mol. weight) in lysates of COS7 cells transfected with brain-derived neurotrophic factor gene. These indicated that both antibodies predominantly recognized identical precursor protein(s) or its derivative(s) probably because of their much higher amts. than the amount of mature protein. Immunochem. studies showed that anti-V2 predominantly stained the cytoplasm of cells; whereas the anti-V4 bound to the nucleus, suggesting that the tertiary structure of immunoreactive mols. changed depending on their location. Cell populations with the immunoreactivity were similar in most brain sections stained with either anti-V2 or anti-V4 antibodies. These results suggest that brain-derived neurotrophic factor-like immunoreactivity distributes, in most cases, in neurons responding to brain-derived neurotrophic factor and in neurons expressing abundant brain-derived neurotrophic factor mRNA. These, taken together with other results concerning distributions of mRNAs of brain-derived neurotrophic factor and TrkB, provide addnl. information to elucidate the function of brain-derived neurotrophic factor in the rat central nervous system.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:324904 HCAPLUS
DOCUMENT NUMBER: 127:29250
TITLE: Administration of corticosterone alters intracellular localization of brain derived neurotrophic factor-like immunoreactivity in the rat brain
AUTHOR(S): **Nitta, Atsumi**; Fukumitsu, Hidefumi; Kataoka, Hiroshige; Nomoto, Hiroshi; **Furukawa, Shoei**
CORPORATE SOURCE: laboratory Molecular Biology, Gifu Pharmaceutical University, Gifu, 502, Japan
SOURCE: Neuroscience Letters (1997), 226(2), 115-118
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the distribution of immunoreactivity for brain-derived neurotrophic factor (BDNF) in rat brain after peripheral administration of corticosterone or vehicle. In the immunohistochem. study, BDNF-like immunoreactivity (LI) was observed predominantly in the nucleus of the cortical and hippocampal neurons in the brain of vehicle-treated rats. In corticosterone-treated rats, BDNF-LI was markedly reduced in the nucleus and concomitantly increased in cytoplasm. Western immunoblot study also demonstrated that corticosterone significantly reduced BDNF-LI in the nuclear fraction of the cerebral cortex and hippocampus. These results indicate that corticosterone regulates the intracellular localization of BDNF and/or its derivs. in the rat brain.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:168970 HCAPLUS

DOCUMENT NUMBER: 126:233522
TITLE: Oral administration of propentofylline, a stimulator of nerve growth factor (NGF) synthesis, recovers cholinergic neuronal dysfunction induced by the infusion of anti-NGF antibody into the rat septum
AUTHOR(S): **Nitta, Atsumi**; Ogihiara, Yoshiko; Onishi, Joji; Hasegawa, Takaaki; **Furukawa, Shoei**; Nabeshima, Toshitaka
CORPORATE SOURCE: Dep. Neuropsychopharmacology Hosp. Pharm., Nagoya Univ. Sch. Med., Nagoya, Japan
SOURCE: Behavioural Brain Research (1997), 83(1/2), 201-204
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have reported that the continuous infusion of anti-nerve growth factor (NGF) monoclonal antibody into the septum of rats produced an impairment of memory and a decrease in choline acetyltransferase (ChAT) and cholinesterase (ChE) activities in the hippocampus. Propentofylline, a xanthine derivative, has potent stimulatory effects on NGF synthesis/secretion in mouse astrocytes in vivo. To investigate the pharmacol. effects of propentofylline in vivo, we induced amnesia in rats by infusing anti-NGF antibody into the septum for 16 days. One group of rats was given no further treatment, while the other group was treated with propentofylline orally once a day for 19 days, commencing 3 days before the implantation of the mini-osmotic pump, and containing thought the period during which the animals performed the behavioral tasks. In the treated amnesic rats, learning and memory in the 3 tasks and ChAT and ChE activity were reduced compared to valued in control rats. The administration of propentofylline recovered the decreased learning capacity and the deficit in cholinergic marker enzyme activity. These results suggest that the use of NGF stimulators may provide a new approach to the treatment of dementia.

L39 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:395087 HCAPLUS
DOCUMENT NUMBER: 125:132427
TITLE: Propentofylline prevents neuronal dysfunction induced by infusion of anti-nerve growth factor antibody into the rat septum
AUTHOR(S): **Nitta, Atsumi**; Ogihara, Yoshiko; Onishi, Joji; Hasegawa, Takaaki; **Furukawa, Shoei**; Nabeshima, Toshitaka
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University School of Medicine, 65 Tsuruma-Cho Showa-Ku, Nagoya, Japan
SOURCE: European Journal of Pharmacology (1996), 307(1), 1-6
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have reported that the continuous infusion of anti-nerve growth factor (NGF) monoclonal antibody into the septum of rats produces neuronal dysfunction in the cholinergic system. Propentofylline has potent stimulatory effects on NGF synthesis/secretion in mouse astrocytes in vitro. To investigate the pharmacol. effects of propentofylline, we used an animal model of dementia in which anti-NGF antibody was infused into the septum for 16 days via a mini-osmotic pump. The rats were treated with propentofylline orally once a day throughout the period during which performance in learning and memory tasks was observed In the vehicle-treated dementia rats, learning and memory ability and choline acetyltransferase

and cholinesterase activity were reduced compared to values in the control rats. The administration of propentofylline prevented the decreased learning capacity and the deficit in cholinergic marker enzyme activities. These results suggest that the use of NGF stimulators may provide a new approach to the treatment of dementia.

L39 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:89120 HCAPLUS
DOCUMENT NUMBER: 124:172498
TITLE: Age-related changes in learning and memory and cholinergic neuronal function in senescence accelerated mice (SAM)
AUTHOR(S): **Nitta, Atsumi**; Naruhashi, Kazumasa; Umemura, Masayuki; Hasegawa, Takaaki; **Furukawa, Shoei** ; Sekiguchi, Fujio; Ishibashi, Kotaro; Nabeshima, Toshitaka
CORPORATE SOURCE: Dep. Neuropsychopharmacologyy and Hospital Pharmacy, Nagoya Univ. School Medicine, Nagoya, 466, Japan
SOURCE: Behavioural Brain Research (1995), 72(1/2), 49-55
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The senescence-accelerated mouse (SAM) has been established as a murine model of accelerated aging. The authors investigated learning ability and memory in various tasks in a SAM strain, SAMP1TA, and in control strain of SAMR1TA at the ages of 20, 30, and 40 wk. The authors also measured choline acetyltransferase (ChAT) and cholinesterase (ChE) activity in the brains of these mice at the same ages. In a Y-maze task, in which short-term memory can be examined, there was no difference in learning ability between SAMP1TA and SAMR1TA at any age. Ability in latent learning and passive-avoidance tasks was less in SAMP1TA at 30 wk of age than in age-matched SAMR1TA. The level of ChAT activity in the striatum of SAMP1TA was lower, than that of SAMR1TA at the ages of 20 and 30 wk. At the ages of 40 and 50 wk, ChE activity in the striatum of SAMP1TA was lower than that of SAMR1TA. These results suggest that SAMP1TA has a deficit, with cholinergic neuronal dysfunction, in learning ability and memory, as shown by impairment of performance in latent learning and long-term memory, but not in short-term memory.

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L21 1 SEA FILE=REGISTRY ABB=ON PLU=ON "N-ACETYL-L-PIPECOLIC ACID"/CN
L22 SEL PLU=ON L21 1- CHEM : 3 TERMS
L23 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L22
L24 382 SEA FILE=REGISTRY ABB=ON PLU=ON PIPECOLIC
L25 4330 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 OR PIPECOL?
L26 383 SEA FILE=REGISTRY ABB=ON PLU=ON NEUROTROPHIN?
L27 12485 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 OR ?NEUROTROPHIN? OR NEUROTROPHIC FACTOR?/CV
L28 23 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L27
L29 137170 SEA FILE=HCAPLUS ABB=ON PLU=ON NEURODEGENERAT?/CV OR ALZHEIMER?/CV OR PARKINSON?/CV OR (HEAD OR SPINAL)(2A)(TRAUMA OR INJUR?) OR HUNTINGTON?/CV OR CEREBRAL INFARCTION? OR MULTIPLE SCLEROSIS?/CV OR AMYOTROPH?/CV OR ALS OR DIABET?/CV OR NEUROPATH?/CV
L30 465718 SEA FILE=HCAPLUS ABB=ON PLU=ON "NERVE, DISEASE"/CV OR NERVE(2A)DISEASE OR ?NEURODEG? OR ?ALZHEIMER? OR ?PARKINS? OR ?HUNTINGTON? OR ?INFARCT? OR ?SCLEROSIS? OR ?DIABET? OR

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                ?NEUROPATH? OR ?SENIL? OR ?DEMENTI? OR MEMORY
L32           55 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25(L)(L29 OR L30)
L33         4154 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND PD=<NOVEMBER 10, 2004

L35           68 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L32 OR L28) NOT L23
L36           62 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L35
L37          374 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "FURUKAWA SHOEI"/AU OR
                FURUKAWA S/AU
L38          121 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "NITTA ATSUMI"/AU OR NITTA
                A/AU
L40            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L37 OR L38) AND L25) NOT
                (L23 OR L36)


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